STUDIES in the INDOLE SERIES.

by

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CONTENTS.

GENERAL INTRODUCTION.

In the sweeping advance of a rapidly develop-:ing science, with its constantly changing foci of major interest, it is perhaps inevitable that numerous problems should be left behind for succeed-:ing generations to elucidate. Such a problem is represented by the mechanism of Emil Fischer's well-known synthesis of indole derivatives by the deamination of aryl hydrazones, and it was with the intention of testing one of the theories of the course of this reaction that this investigation was commenced.

To enable this to be done it was necessary to utilise derivatives of indole containing a substituent in the benzene ring. The isomeric Bz-methyl homologues of α-phenyl indole were chosen for this purpose as being the most convenient. Two of the four isomers were already known, a third has now been prepared, and the remaining member of the group obtained in the form of derivatives. It was further necessary to isolate several new characterising derivatives of these indoles in order that any given one could be identified with certainty, as it was found that the compounds previously used for this purpose were highly unsatisfactory.

As a result of these investigations a further problem presented itself - the structure of the indole/

indole "nitroso-compounds". In addition, the opportunity was also utilised to make a critical comparison of the relative values of the various methods available for the preparation of the indole derivatives dealt with in the course of this work.

The thesis therefore falls naturally into three main parts as indicated on the contents page. The first deals with the preparation of α-phenyl indole and its Bz-methyl homologues, four different methods being investigated and compared. A series of characterising derivatives has also been prepared for each of the five indoles.

Part II deals with the mechanism of the Fischer indole synthesis, the two chief theories being examined experimentally, and the whole subject discussed in some detail.

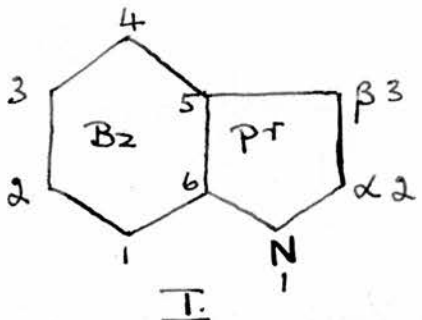
Part III is devoted to the question of the "nitroso-compounds", especially those of the indoles prepared in this research.

Each part is divided into three sections; introduction, experimental and discussion. The first deals with previous work only, the second embraces the present experiments and any detailed discussion arising as a result thereof, while the discussion is reserved for a more general survey of the subject under examination.

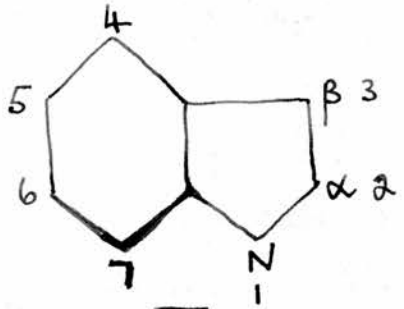
Finally, a conclusion and summary is appended in which the main outlines of the work are brought together./

together.

NOTE:- For the numbering of the indole ring two systems have been used; the original system of Baeyer (I) and the modern one due to Fischer (II).



I.



II.

The latter system is employed exclusively to-day, but most of the older papers use the Baeyer numbering, relics of which are still retained in expressions such as "Bz-methyl homologues", the prefix being derived from Baeyer's practice of numbering the benzene and pyrrole rings separately, and indicating the one referred to by means of the respective prefixes Bz (or B) and P^r.

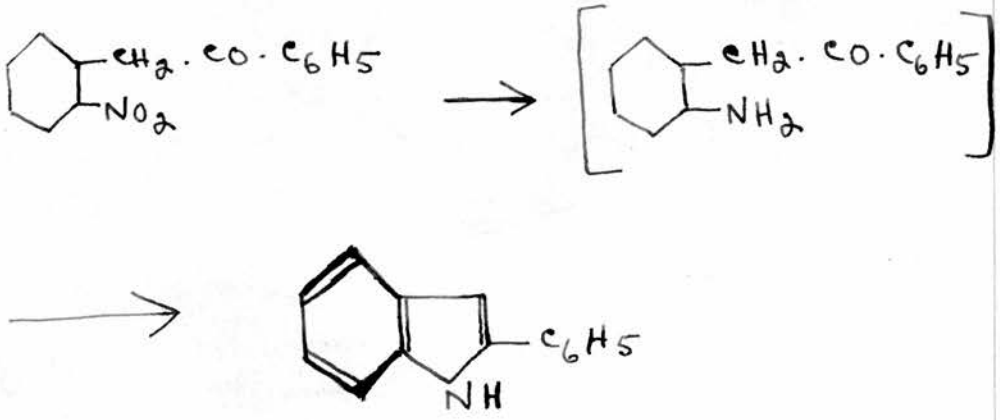
PART I. The Preparation, Identification and Characterisation of α-Phenyl Indole and its Bz-methyl Homologues.

INTRODUCTION:

These substances can be made by four distinct methods, two of which embrace several quite different modifications.

(1) Reduction of aromatic nitro-compounds containing a suitable side-chain in the ortho-position frequently gives rise to indole derivatives by the elimination of water between the resultant amino-group and the side-chain, and subsequent ring closure.

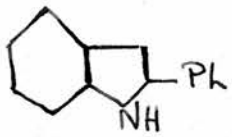
E.g. The reduction of ortho-nitrodesoxybenzoïn yields α-phenyl-indole (Pictet, Ber., 1885, 19, 1064)



(2) Bischler's method consists in heating an anilide with an amine (Ber., 1892, 25, 2860)

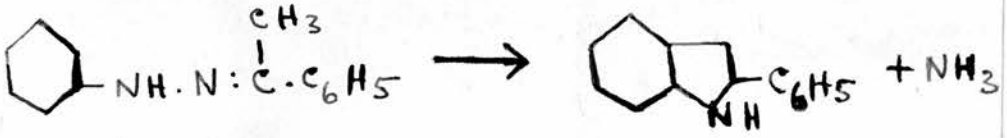
E.g. α-Phenyl indole is produced by boiling phenacylanilide with aniline.

$$Ph.CO.CH_2.NH.C_6H_5 + NH_2.C_6H_5 \longrightarrow Ph.\underset{\underset{NH.C_6H_5}{|}}{C}:CH.NH.C_6H_5 + H_2O$$

$$\longrightarrow$$  $$+ NH_3.C_6H_5$$

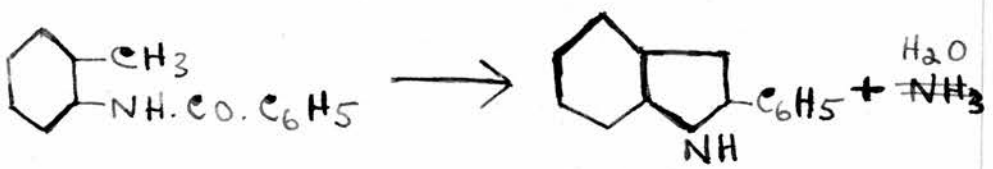
(3) Fischer's method makes use of the aryl hydrazones of aldehydes, ketones and keto-acids of the type $R.CO.CH_2R'$. These substances, under the influence of various catalysts, lose ammonia with the production of indole derivatives.

E.G. Acetophenone-phenylhydrazone, when fused with zinc chloride at 180°, gives α-phenyl indole. (Fischer, Ann., 1886, 236, 116)



(4) Madelung's method involves the dehydration of ortho-substituted acyl amines by means of sodium ethoxide, sodium amyloxide or alkaline earth oxides at a high temperature (360°), in absence of air.

For example, α-phenyl indole is obtained from benzoyl-o-toluidine (Madelung, Ber., 1912, 45 (1), 1131).



Other workers have used different dehydrating agents. For example, Verley (Bull. Soc. Chim., 1924, 35, 1039; 1925, 37, 189) uses a fusion with sodamide, while/

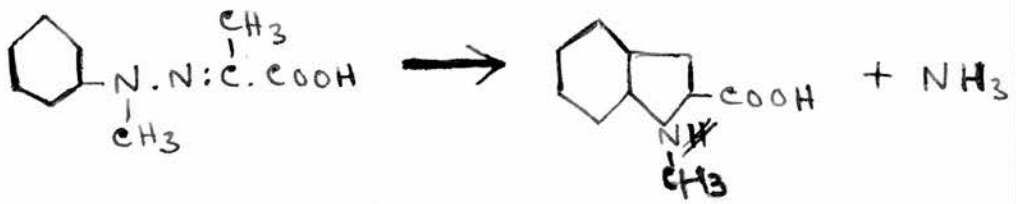
while Imperial Chemical Industries have patented a process utilising the action of alkali metals on the acylated amines suspended in inactive solvents such as diethylaniline and tetrahydronaphthalene (British Abstracts, B, 1930, 809).

The method of Pictet was not used in this research as numerous difficulties were forseen in applying it to the preparation of the Bz-methyl homologues of α-phenyl indole. As these substances could be prepared much more easily by Fischer's method, it was considered preferable to leave Pictet's process for later examination.

Bischler's method is discussed in the experimental section (page 18).

By far the easiest and most convenient though probably not the cheapest, method for the preparation of indole derivatives was found to be that of Fischer.

The discovery of this reaction arose from the chance observation (Fischer and Jourdan, Ber., 1883, 16, 2245) that the hydrazone of methylphenylhydrazine and pyruvic acid was not hydrolysed to the parent hydrazine and keto-acid on boiling with dilute aqueous hydrochloric acid, but was converted, by loss of ammonia, into a substance which was later identified as a derivative of indole, namely 1-methyl indole-2-carboxylic acid:



This formation of an indole by loss of ammonia was soon shown to be a general property of aryl hydrazones of the type $Ar.NH.N:CR.CH_2R'$, the essential requirement being the presence of a $-CH_2-$ group in the α-position to the keto- or aldehyde group of the ketone, keto-acid or aldehyde from which the hydrazone was prepared.

Only in a few cases, however, could the reaction be carried out by the use of aqueous hydrochloric acid. This method served for the hydrazones of certain α-substituted aryl hydrazines ($Ar.NR.NH_2$), but not for the majority of unsubstituted hydrazines ($Ar.NH.NH_2$). The latter could only be converted into indole derivatives by fusing them with zinc chloride at a high temperature.

This latter procedure is the one generally used now as it is of almost universal applicability, thus differing from the other modifications of the process.

The yield of indole obtained in a zinc chloride fusion depends on the particular hydrazone used, and varies widely from 30% to almost 100%. The fusion temperature required also varies widely from 130° to 280°. This treatment, of course, is very drastic, and failure to obtain any required indole by this method probably means that for steric or other reasons the hydrazone used is incapable of forming the indole.

Less drastic conditions serve to produce indoles/

indoles from many hydrazones; for example, boiling them with hydrochloric acid (aqueous or alcoholic), glacial acetic acid, sulphuric acid or phosphoric acid often suffices. These methods, it appears, are only applicable to hydrazones of easily enolizable ketones, etc. (see page 136).

It is further generally observed that indole formation takes place very much more easily with hydrazones which yield either 2:3-disubstituted indoles or N-substituted indoles.

For example, the methylphenylhydrazone of pyruvic acid yields N-methyl indole 2-carboxylic acid (see above) when boiled with aqueous hydrochloric acid, whereas the unsubstituted phenylhydrazone only yields indole-2-carboxylic acid when fused with zinc chloride at 180°. (Fischer, Ber., 1886, 19, 1563).

It is also observed that various reactions of naphthalene derivatives, which are really further examples of the Fischer synthesis, proceed with much greater readiness than is usual in the benzene series. Many of these reactions are brought about smoothly and easily by means of glacial acetic acid, sulphuric acid, phosphoric acid or hydrochloric acid.

Some examples of this kind are referred to in connection with the theoretical discussion on the mechanism of the Fischer indole synthesis (pages 134 and 140).

In the fusion process other catalysts than zinc/

zinc chloride have been successfully utilised. It has long been known, for example, that stannous chloride gives almost as good yields as the zinc salt, at least in certain cases.

More recently, Korczynski and Kierzek (Gazz., 1925, 55, 361) have investigated the catalytic activity of powdered metals and of metallic chlorides in producing indoles from hydrazones, and have shown that nickel, cobalt and copper are effective catalysts in a concentration of 1%, while iron, zinc, aluminium, tungsten, titanium, uranium and molybdenum have little or no effect.

Besides zinc chloride and hydrochloric acid, these investigators found that the chlorides of nickel, copper, chromium and uranium were useful catalysts in many cases, but that they were not so in all.

Nickel chloride alone gave a better yield than zinc chloride, the other chlorides giving poorer yields. Unfortunately, nickel chloride was found to be less generally applicable than the zinc salt, and failed in certain important cases to effect the synthesis (see below).

Korczynski and Kierzek therefore conclude that the best catalyst in a Fischer fusion is nickel chloride, where that substance is effective, and zinc chloride in all other cases.

Apparently, however, the use of nickel chloride requires a higher fusion temperature, and this, on

account/

account of the general instability of hydrazones and the prevalence of charring, is not to be desired. Moreover the yield quoted by the above investigators for α-phenyl indole, using nickel chloride as catalyst, is inferior to the yield actually obtained, in this research at least, by the use of zinc chloride. (N.B. A most unsatisfactory feature of the older work on indoles is the failure to quote yields, thus making comparisons of the different methods impossible without personal experiment.)

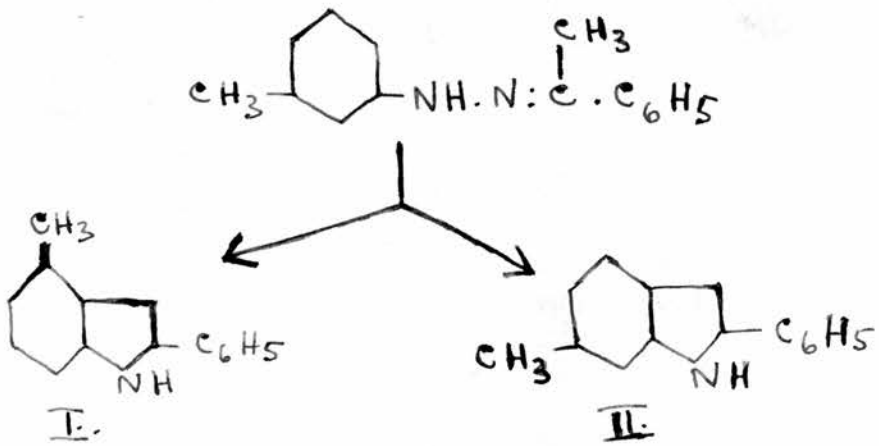
An important failure of the nickel chloride fusion was observed by Korczynski and Kierzek (loc. cit.) and again later by Korczynski, Brydowna and Kierzek (Gazz., 1926, 56, 903,) in the case of para-halogenated hydrazones. These did not give 5-halogenated indole derivatives but underwent pro-:found decomposition in all cases examined. Fusion with zinc chloride, however, does yield the required indole, many 5-chloro-indoles being the subjects of patents.

The use of alcoholic hydrochloric acid as a catalyst in the Fischer synthesis (Trennkler's method) is discussed in the experimental portion (page 26).

EXPERIMENTAL.

Four methods of preparing indoles were investigated — those of Bischler, Fischer, Trennkler and Madelung (see above).

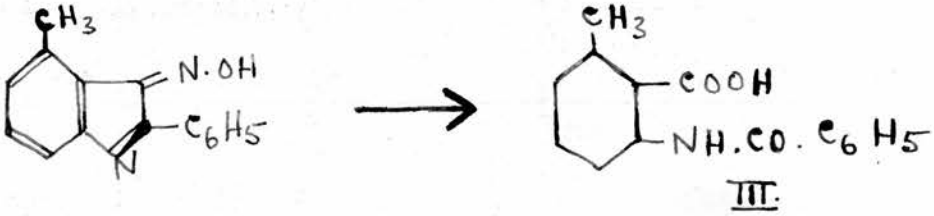
It was found that the particular indoles required in this research could not be made success-:fully by Trennkler's process. The other three methods all gave the desired compounds, but with varying degrees of efficiency. The Fischer synthesis was found to be easily the best, and by this means were prepared α-phenyl indole, α-phenyl-p-toluindole and α-phenyl-m-toluindole. The first two compounds were previously known, but the third was both new and of uncertain constitution, since the substance from which it was prepared, acetophenone-m-tolylhydrazone, could give either α-phenyl-4-methyl indole (I) or α-phenyl-6-methyl indole (II).



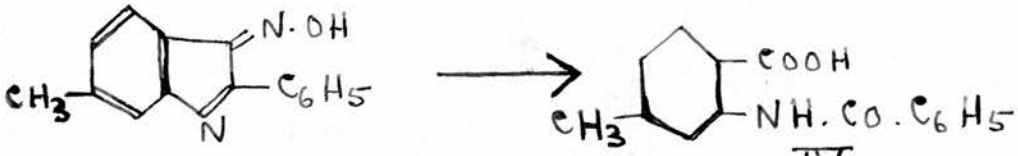
I. II.

Actually only one indole was obtained. An attempt was therefore made to orientate the methyl group by oxidising the iso-nitroso compound of the indole to a methyl benzoyl-anthranilic acid, whose structure could be determined by comparing it with the/

the two substances III and IV below. These compounds are not described in the literature and were therefore synthesised for this purpose.



III.



IV.

In this way it was hoped to establish a general method for orientating substituents in the benzene ring portion of indole derivatives. In the present case, however, the method was only partially successful on account of the unanticipated oxidation of the methyl group to carboxyl, with production of a compound which decomposed at a high temperature without melting, and was thus impossible to identify with certainty. Details of this work are given in the following pages.

A definite proof of the structure of the α-phenyl-m-toluindole was obtained by synthesising 2-phenyl-4-methyl indole and 2-phenyl-6-methyl-indole by Madelung's method, when the latter compound was identified as the α-phenyl-m-toluindole already prepared. The Madelung synthesis thus served the dual purpose of orientating the methyl group in the α-phenyl-m-toluindole obtained by both Fischer's method/

method and Bischler's method, and of furnishing the second α-phenyl-m-toluindole, which cannot be obtained by these methods because of preferential formation of the 6-methyl derivative.

The Fischer method was also used to prepare 1-methyl-2-phenyl indole, a compound required in the investigations into the structure of the "nitroso-compounds" of the indoles. The preparation of this substance is described in Part III page 203. It was found that the remaining indole required, α-phenyl-o-toluindole, could not be made by Fischer's method, since decomposition and charring of the hydrazone always occurred in preference to indole formation. The substance was obtained, however, by Bischler's method.

Finally, α-phenyl indole was prepared by the processes of Madelung, Bischler and Fischer, and the respective yields found to be 4·5%, 16% and 70% of the theoretical, a comparison which shows at once the relative values of the methods.

A. Preparation of Indoles by Bischler's Method.

(1) Preparation of ω-bromacetophenone.

Mŏhlau, Ber.,1882, 15, 2464.

Acetophenone (100 gms.) was dissolved in 500 gms. glacial acetic acid, and 133·5 gms. bromine added slowly from a dropping-funnel, with vigorous mechanical stirring. The resultant mixture was allowed to stand for one hour and was then heated gently on the water-bath until colourless, whereupon it was poured into a large volume of water. A greenish-yellow oil separated, which solidified after standing for 24 hours. This was filtered off, pressed well on porous plate and recrystallised from alcohol.

The substance was obtained as greyish scales melting at 50° (Mŏhlau, loc. cit. quotes 50°).

$$C_6H_5.CO.CH_3 + Br_2 \longrightarrow C_6H_5.CO.CH_2Br + H\ Br$$

The yield obtained was 97 gms. representing 59% of the theoretical.

(2) Preparation of phenacylanilide.

Bischler, Ber.,1892, 25, 2860.

$$C_6H_5.CO.CH_2Br + 2\ H_2N.C_6H_5 \longrightarrow C_6H_5.CO.CH_2.NH.C_6H_5 + C_6H_5.NH_2,H\ Br.$$

37 gms. aniline

40 gms. bromacetophenone.

The aniline was dissolved in twice its volume of alcohol and the bromacetophenone added. The latter substance was dissolved by stirring, and the resultant clear solution set aside at room temperature. A gentle reaction soon commenced and the anilide separated out from the solution as yellow crystals, which were filtered off and used without further purification for the preparation of the indole. The substance was contaminated with aniline hydrobromide but this was not removed as it was found to be an essential catalyst for the next reaction - the preparation from it of α-phenyl indole.

For this purpose the impure anilide had to be used at once as it turned red rapidly in air. If, however, it was washed with alcohol and recrystallised once from this solvent, it was obtained pure in the form of yellow glistening needles or long plates, melting at 95°, as compared with Mühlau's quotation, 93° (Ber., 1882, 15, 2480).

The pure substance was perfectly stable in air and was obtained in a yield of 19 gms., or 45% of the theoretical.

(3) Preparation of phenacyl-o-toluidide.

This was prepared exactly as above for phenacylanilide, using 43 gms. ortho-toluidine and 40 gms. bromacetophenone.

The yield obtained was 31 gms., or 69% of the theoretical. After one light wash with alcohol, the

substance/

substance melted at 87°-88°, and after recrystallis-:ation from this solvent at 89°. (~~Möhlau~~ BISCHLER, loc. cit., quotes 89°)

(4) Preparation of phenacyl-p-toluidide.

30 gms. bromacetophenone.

33 gms. p-toluidine.

The method described above was again used, and a yield of 34 gms. of practically pure substance was obtained (100% theory).

On recrystallising from alcohol, the compound was obtained as long, flat, rectangular plates melting at 124°-127°.

Lellmann and Donner (Ber., 1890, 23, 167) quote the melting-point as 134°, and state that the product obtained by the above method contains some diphenacylparatoluidide $(C_6H_5.CO.CH_2)_2 : N.C_6H_4.CH_3$, which they removed as follows:-

The toluidide was dissolved in hot concentrated hydrochloric acid, and filtered from the insoluble diphenacyl-p-toluidide. The mono-phenacyl-p-toluidide was precipitated from the filtrate by neutralisation with sodium hydroxide, and was filtered off, dissolved in hot alcohol, filtered from any traces of diphenacyl-p-toluidide which may have dissolved in the acid, and the hot alcoholic solution allowed to crystallise. In this way they prepared a substance melting at 134°.

Similar treatment, however, of the substance obtained/

obtained in this research yielded a product of unchanged melting-point, 124°-127°. On further recrystallisation from alcohol, the melting-point 127° was obtained, in agreement with Bischler (Ber., 1892, 25, 2860), who apparently was unaware of the work of Lellmann and Donner, and purified his phenacyl-p-toluidide merely by recrystallisation from alcohol. This treatment would remove any diphenacyl-p-toluidide, which is insoluble in the solvent employed and would presumably have been filtered off before the solution was allowed to crystallise.

(5) Preparation of phenacyl-m-toluidide.

This substance was made in precisely the same way as the corresponding ortho and para compounds. It has not been made before.

A yield of 108 gms. was obtained from 97 gms. bromacetophenone and 104 gms. m-toluidine, this representing 98% of the theoretical.

The substance was obtained completely pure by one recrystallisation from alcohol, and melted at 110°. It was obtained as long flat prisms insoluble in water and petrol ether, but easily soluble in benzene, acetone, carbon disulphide, ether, glacial acetic acid and chloroform.

Nitrogen analysis (Ter Meulen):-

Found	N 6·22%
Calculated	N 6·22%

Preparation of Indoles.

Bischler, Ber., 1892, 25, 2860.

Each of the four anilides was boiled, in a flask fitted with a short reflux air-condenser, with four times its weight of the particular amine used in its preparation.

The mixture was boiled for various lengths of time, the condenser allowing water to escape but returning the amine to the flask. The product was then poured into water containing sufficient hydrochloric acid to keep all the amine in solution as the hydrochloride. The resultant yellowish solid was removed by filtration, dried as well as possible, and then distilled in vacuo using an Anschütz flask. According to Bischler, the three indoles made by him distil at 250°- 260° at 10 m.m. pressure.

The crude indoles were easily obtained, and in such amount as to promise excellent yields, but the method of purification by distillation in vacuo was found to be highly unsatisfactory.

Even at 250° these indoles possess such a low vapour pressure that they distilled with extreme slowness, and considerable decomposition took place, with production of a thick, black, viscid sludge which could not be prevented from bumping heavily, the precautions usually adopted to prevent this being of little service on account of the viscosity of the tarry material.

Because of this difficulty, Bischler's method was abandoned in favour of Fischer's, except in the case of 2-phenyl-7-methyl indole, which, it was found, could not be prepared by the latter process.

It is noteworthy that Bischler only quotes yields of crude products, and not those after distillation, and that his method has not been patented like those of Fischer and Madelung.

In confirmation of Bischler's own observation, it was found that the crude indoles could not be purified by recrystallisation, as a semi-solid product was always obtained which would not solidify properly.

Sometimes the substance obtained on pouring the reaction mixture into water was of a soft tarry consistency and only solidified with great difficulty after long standing. This was found to be due to insufficient boiling.

It was also found that an essential catalyst for the formation of the indoles was hydrochloric (or hydrobromic) acid. Normally the latter acid was found as an impurity in the anilide used, provided that this had not been washed with alcohol or other-:wise purified before use. In the absence of this catalyst not a trace of indole was formed. For example, on boiling pure phenacyl-m-toluidide with m-toluidine for 48 hours, the resultant product failed to give the pine-splint reaction and so con-:tained no indole.

(6) Preparation of α-phenyl indole.

20 gms. phenacylanilide.

80 gms. aniline.

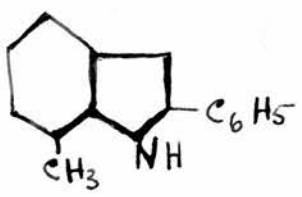
These were boiled for two hours and the reaction mixture poured into dilute hydrochloric acid (250 c.c. 2 N. acid + 200 c.c. water). The precipitated solid was filtered off and unsuccessful attempts made to recrystallise it from alcohol and from carbon disulphide. In the former case a semi-solid material was always obtained, and in the latter case at least 80% of the indole was lost in the mother-liquor on account of the great solubility of α-phenyl indole in carbon disulphide. A few good cubic crystals were obtained, however, melting at 187·5°.

The mother liquor was evaporated to dryness and the residue distilled in vacuo. The yield of raw product before distillation was 13 gms., but the distillate only amounted to 3 gms., or 16% of the theoretical yield.

The indole distilled as a pale yellow oil, which solidified at once and showed a melting-point of 184°. After recrystallisation from alcohol, it melted at 187°.

(7) Preparation of α-phenyl-o-toluindole.

(2-phenyl-7-methyl indole)



30 gms. phenacyl-o-toluidide.

120 gms. ortho-toluidine.

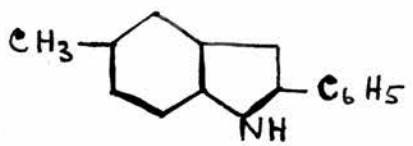
The method used was exactly as above. The crude product formed a solid yellow cake, which, on distillation in vacuo, gave 12 gms. of substance melting at 109°-114°. Recrystallisation from alcohol gave 9 gms. of indole melting at 116°. The hard, white, glistening crystals so obtained, after a second recrystallisation, melted at 117° as compared with Bischler's quotation, 118°-119°.

Despite considerable bumping, which twice resulted in heavy loss of material, the yield of fairly pure indole (12 gms.) amounted to 43% of theory.

Possibly the greater ease of distillation of this indole as compared with the other three is due to the fact that its melting-point lies 80° lower than any of the others, and that therefore, presumably the viscosity of the liquid at 250° is less than in the other cases.

(8) Preparation of α-phenyl-p-toluindole.

(2-phenyl-5-methyl indole).



The same method and quantities were used as in the last preparation described, the mixture of anilide and toluidine being boiled for 35 minutes (although/

(although Bischler merely heated to the boiling-point). The mixture turned almost black, but no charring occurred. The product obtained, however, by pouring the reaction mixture into dilute hydro-:chloric acid did not show the pine-splint reaction and gave no yellow "nitroso-compound" when dissolved in glacial acetic acid and treated with solid sodium nitrite (see below). It therefore contained no indole, probably because the phenacyl-p-toluidide used was too pure and did not contain sufficient hydrobromic acid.

To obviate this difficulty the indole was made directly from bromacetophenone and para-toluidine. The reactants, 10 gms. of the former and 20 gms. of the latter, were mixed in a flask fitted with a short reflux air-condenser. On heating gently a vigorous reaction commenced and dense fumes of hydrobromic acid were liberated. When this initial phase had subsided, the mixture was boiled gently for two hours. As before, the product was poured into dilute hydro-:chloric acid, and the resultant solid filtered off and dried. This substance gave a strong pine-splint reaction.

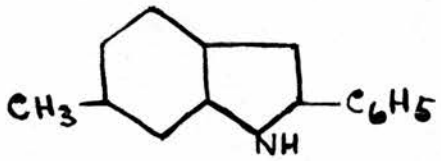
The yield of crude indole was 10 gms., the theoretical yield being 10·5 gms.

Despite every precaution it was found almost impossible to distil the crude product successfully, and as the indole was now obtained with great ease by the/

the Fischer process (see page 41) this method was abandoned after one unsuccessful attempt at distill-:ation.

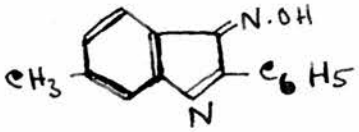
(9) Preparation of α-phenyl-m-toluindole.

(2-phenyl-6-methyl indole)

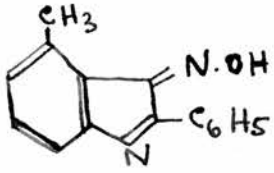


This was prepared in precisely the same way as the corresponding para compound described on page 21, using 10 gms. bromacetophenone and 20 gms. meta-toluidine. Instead of distilling the crude product, however, it was converted into the iso-nitroso-compound by dissolving it in glacial acetic acid and treating with solid sodium nitrite. On pouring into water, a dirty yellowish-brown precipitate was formed, which was filtered off, washed successively with water and alcohol, and then recrystallised from amyl acetate. A yield of 6 gms. was obtained, this representing 50% of the theoretical. The substance melted at 231° with decompcsition, and after a second recrystallisation from amyl acetate at 236° (decomposition). A third recrystallisation did not raise the melting-point.

As is explained below, this substance, from its method of synthesis, may possess either of the two formulae



or



The same is true for the iso-nitroso- compound of the α-phenyl-m-toluindole made by Fischer fusion from acetophenone-m-tolylhydrazone (page 41). These two substances, however, possessed the same melting-point, and a mixed melting-point showed no depression.

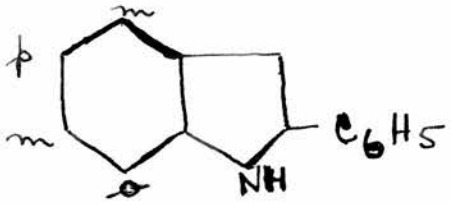
The two compounds were also acetylated (page 110), and the resultant products shown by melting-point and mixed melting-point to be identical.

This therefore proved that the α-phenyl-m-toluindole made by Bischler's method was the same as that made by Fischer's method.

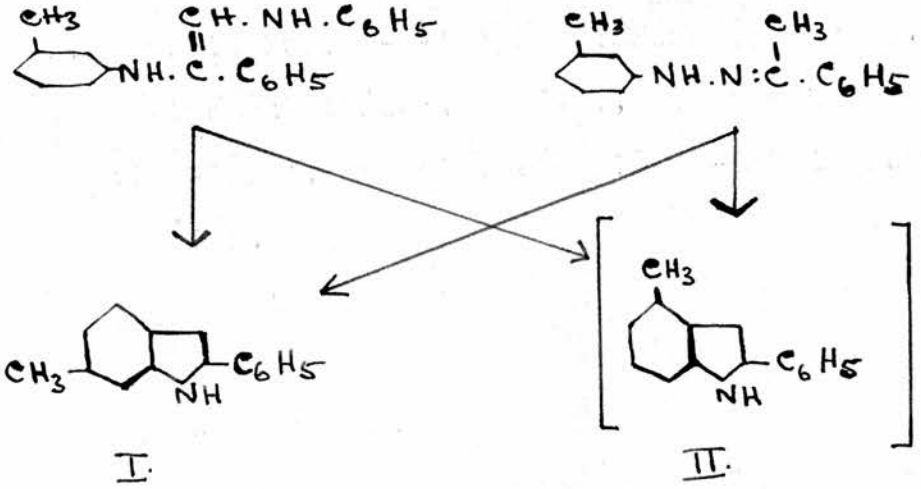
The formulation of two possible α-phenyl-m-toluindoles may be explained as follows:-

In the preparation of the above three methyl indoles by either Bischler's method or Fischer's method (see below), the only information given by the synthesis regarding the position of the methyl group is that it is in the Bz-ring, and either ortho, meta or para to the imino-group of the indole ring, according to whether we start with ortho-,meta- or para-toluidine.

In the cases of the ortho and para compounds this is sufficient to define the position of the methyl group, but in the case of the meta compound two positions are possible:-

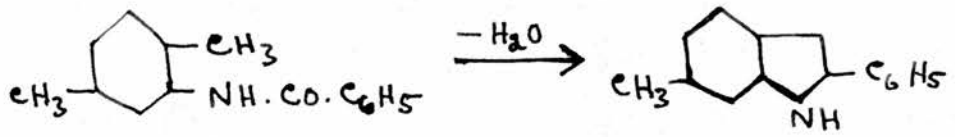


α-Phenyl-m-toluindole may therefore be either the 4-methyl compound (II) or the 6-methyl isomer (I).



I. II.

The formulation of the substance as 2-phenyl-6-methyl indole (I) is based on its synthesis (described later) from benzoyl-p-xylidine by Madelung's method (page 66).



B. Preparation of Indoles by Trennkler's Method.

Ann., 1888, 248, 106.

This is merely a modification of the ordinary Fischer synthesis of indoles from hydrazones, in that the reaction is carried out in alcoholic solution using dissolved hydrochloric acid as catalyst, instead of being carried out as a high temperature fusion using zinc chloride as catalyst.

The method, however, is not universally applicable, and even in those cases where it is, practical difficulties often render it unsuitable. On the other hand, there is no doubt that in many cases the method does give much larger yields than the zinc chloride fusion. According to Korczynski, Brydowna and Kierzek (Gazz., 1926, 56, 903) two difficulties are associated with this method. Firstly, in presence of hydrochloric acid many indoles undergo polymerisation. Secondly, unless the alcohol is removed immediately the indoles are formed, emulsions are produced which render purification difficult.

The phenyl-indoles do not polymerise, however, but in the two cases examined in this research, the rate of formation of indole (as estimated visually from the amount of ammonium chloride precipitated) was so slow that the second difficulty automatically arose.

Acetophenone-m-tolylhydrazone (see page 37) was/

was added to a saturated solution of hydrochloric acid in alcohol. A deep purple solution was immediately produced and the mixture was heated under reflux on the steam-bath for two days. A white precipitate of ammonium chloride separated slowly. When it was observed that the precipitate was not increasing, water was added and the alcohol driven off on the steam bath. The dark purple residue was now extracted with ether, the ether layer separated, and evaporated to dryness. A black residue remained which gave the pine-splint reaction but was not worth distilling on account of the small yield.

The preparation was repeated twice with the same result.

An attempt to prepare 1-methyl-2-phenyl indole from acetophenone-methylphenylhydrazone by this method also led to an unsatisfactory result.

Since, therefore, the two indoles in question were much more easily obtained by Fischer fusion, the Trennkler method was abandoned.

The failure of the method was not surprising, as the hydrazones employed were of the type which give indoles least readily - namely, those formed from ketones which are not easily enolisable (see page 136).

Trennkler himself only obtained 2:3-disubstituted indoles by his method, and used the zinc chloride fusion for the preparation of Pr-mono-:substituted/

Pr-monosubstituted derivatives, which, presumably, could not be made by the action of alcoholic hydrochloric acid on the corresponding hydrazones.

Fischer's abandonment of his original method - boiling the hydrazone with dilute aqueous hydrochloric acid - was due to his discovery that the hydrazones of primary hydrazines with pyruvic acid were either hydrolysed into their components by such treatment or were not affected at all (Ber., 1886, 19, 1563). The same thing was observed later with the hydrazones of other ketones and keto-acids. (Fischer, Ann., 1886, 236, 116).

C. Preparation of Indoles by Fischer's Method.

(a) Preparation of hydrazines.

These were made from the corresponding amines by diazotisation followed by reduction.

$$R.NH_2 \xrightarrow{HNO_2 + HCl} R.N_2Cl \xrightarrow{\text{reduction}} R.NH.NH_2$$

The latter stage was carried out by means of either -

(1) sulphur dioxide (Fischer, Ann., 1878, 190, 78)
or (2) stannous chloride (V. Meyer and Iecoo, Ber., 1883, 16, 2976)

The yields obtained by the two methods showed somewhat curious variations, as follows:-

Yield/

	Yield by SO_2 method	Yield by $SnCl_2$ method
o-Tolylhydrazine	28%	41%
m-Tolylhydrazine	39%	25%

The statement of Gallinek and Richter (Ber., 1885, 18, 3175) that the two methods were equally effective, was therefore not substantiated. Further evidence on the point was unobtainable from the literature on account of the consistent failure of authors to quote yields.

For the preparation of even moderate quantities of hydrazines, the stannous chloride method was considered by the present author to be far inferior to the other, on account of the enormous quantities of stannous chloride and hydrochloric acid used in comparison with the amount of hydrazine obtained.

(1) Preparation of o-Tolylhydrazine.

(Fischer's method)

Clarke's "Organic Syntheses" Vol.II, Page 71.

Concentrated hydrochloric acid (105 c.c.) was cooled to 0° in a round-bottomed flask surrounded by ice and fitted with a mechanical stirrer. Ice (50 gms.) was added, and then, with stirring, 43 gms. of ortho-toluidine. Another 50 gms. of ice were now added, and a solution of 29 gms. of sodium nitrite in 60 c.c. of water run in slowly from a dropping-funnel, the solution being kept at 0° by adding more ice from time to time.

Meanwhile,/

Meanwhile, a solution of sodium bisulphite was prepared by passing sulphur dioxide into a well-cooled solution of 89 gms. sodium hydroxide (of 90% purity) in 600 c.c. water, until the solution turned green, or until a little phenolphthalein added remained colourless. This solution was cooled to 5°, stirred vigorously, 50 gms. of ice added, and the diazo solution run into it as rapidly as was consistent with keeping down the temperature.

When all the diazo solution had been added, the mixture was heated to 70° for half an hour, until the mixture became quite dark. The solution was now acidified with concentrated hydrochloric acid and heated for 4-6 hours or overnight until nearly colourless. It was then mixed with one third of its volume of concentrated hydrochloric acid and cooled in a freezing mixture.

The resultant precipitate of o-tolylhydrazine hydrochloride was filtered off, shaken up with 100 c.c. of 25% caustic soda, and the precipitated hydrazine extracted with benzene. The benzene was evaporated off, and the residue distilled in vacuo.

The yield was 13½ gms. or 28% of the theoretical.

(2) Preparation of o-Tolylhydrazine.

(Stannous chloride method)

Ullmann's "Organisch-Chemisches Praktikum"

page/

page 203, (modified)

120 c.c. concentrated hydrochloric acid.

200 gms. ice.

46 gms. ortho-toluidine.

30 gms. sodium nitrite (dissolved in 100 c.c. of water).

The acid and ice were mixed in a litre bolt-head flask surrounded by a freezing mixture and fitted with a mechanical stirrer. The toluidine was added and the sodium nitrite solution run in slowly from a dropping funnel, with vigorous stirring.

The resultant diazo-solution was then poured slowly into a solution of 200 gms. of stannous chloride in 400 c.c. of concentrated hydrochloric acid, kept at 0° and well stirred mechanically.

A grey precipitate (a compound of the hydrazine, hydrochloric acid and stannic chloride, according to Ullmann) formed at once, but this was left overnight before being filtered off and decomposed by shaking up with excess caustic soda solution (100 c.c. of 25% sodium hydroxide). The hydrazine separated partly as an oil but chiefly as a solid.

It was taken up with ether, the ether extract dried over potassium hydroxide, and the ether distilled off. The residue was recrystallised from alcohol when the hydrazine was obtained sometimes as white needles and sometimes as plates, both forms melting sharply/

sharply at 61° as compared with previous quotations 56° and 59° (Bösler, Ann., 1882, 212, 338; Gallinek and Richter, Ber., 1885, 18, 3175).

The yield obtained was 22 gms. or 41% of the theoretical.

(3) Preparation of m-Tolylhydrazine.

(Stannous Chloride method).

The procedure followed was exactly as detailed for the corresponding ortho compound described above, except that after drying the benzene extract of the hydrazine and evaporating off the benzene, the residue was distilled in vacuo.

The yield obtained from 46 gms. of meta-toluidine was 13 gms., representing 25% of the theoretical. The substance distilled as a thick colourless oil which immediately turned pale yellow. It could usually be distilled without decomposition at atmospheric pressure (240°-244°) but it was best distilled in vacuo. It turned red slowly in air and did not solidify at -10°.

The hydrochloride was very soluble in water with the result that the hydrazine could not be made by the usual Fischer method, as this involved precipitation of the hydrochloride from aqueous solution.

It was found, however, that the sulphate was insoluble in cold water though soluble in hot water.

The/

The hydrazine could, therefore, be precipitated as the sulphate.

Thus modified, the Fischer method was found to give a much better yield (39%) than the stannous chloride method (25%).

(4) Preparation of m-Tolylhydrazine.

(Modified Fischer method).

80 gms. meta-toluidine.

200 c.c. concentrated hydrochloric acid.

200 gms. of ice.

54 gms. sodium nitrite (in 110 c.c. of water).

The toluidine was diazotised as described above for the ortho compound, and the resultant diazo-solution added slowly to a well cooled and vigorously stirred mixture of 400 gms. of sodium sulphite crystals, 60 gms. of anhydrous sodium carbonate and 250 c.c. of water. A deep red crystalline precipitate was formed. The mixture was stirred at room temperature until a sample heated in a test-tube no longer became turbid; it was then heated to 30° and reduced by passing in sulphur dioxide. When thoroughly saturated, the mixture was heated to 70° and filtered. The filtrate was mixed with 520 gms. of concentrated sulphuric acid and left overnight to cool. The precipitated m-tolylhydrazine sulphate was then filtered off and treated with excess caustic soda solution, the precipitated oily hydrazine extracted/

extracted with benzene, and isolated as before. It was purified by distillation in vacuo.

The yield obtained was 35 gms., or 39% of the theoretical.

(5) Preparation of p-Tolylhydrazine.

This was obtained in the same way as ortho-tolylhydrazine, by the reduction of diazotised para-toluidine by means of sulphur dioxide.

The hydrazine, after being precipitated from the solution of its hydrochloride, was extracted three times with ether in preference to benzene, the ether evaporated off and the residue (melting-point about 64°) recrystallised from water. The substance was obtained as colourless plates, melting at 66°-67°. (Fischer, Ber.,1876, 9, 890, quotes 61°, and Bamberger, Ber.,1898, 31, 582 gives 65°-66°).

The yield obtained was 62% of the theoretical.

(b) Preparation of Hydrazones.

Usually these were prepared with great ease by heating together in the steam-oven equimolecular quantities of the hydrazine and ketone. The homogeneous mixture soon became turbid by separation of water, the whole solidifying to a mass of crystals on cooling. This was recrystallised from alcohol, in which the hydrazones used in this research are/

are sparingly soluble in the cold and extremely soluble in the hot.

The hydrazones, when filtered off and washed with a little cold alcohol, were obtained as well-defined, slightly yellow crystals, which turned red rapidly in air, but which could be kept for a long time under alcohol. The pure hydrazones were colourless.

$$Ar.NH.NH_2 + OC\begin{matrix}R_1\\R_2\end{matrix} \longrightarrow Ar.NH.N:C\begin{matrix}R_1\\R_2\end{matrix} + H_2O$$

It was observed that the ease of formation of these hydrazones appeared to depend greatly on the state of purity of the hydrazine employed, and probably also on some other factor which was not discovered.

Using freshly distilled pure hydrazines, the formation of hydrazone took place readily in fifteen to thirty minutes, but even slightly impure hydrazines sometimes took several hours. It was definitely found, for example, that m-tolylhydrazine which had not been freshly distilled showed no hydrazone formation even after heating for several days on the steam-bath, although freshly distilled hydrazine gave the hydrazone readily in 20 minutes.

That a second (undetermined) factor probably influenced the rate of hydrazone formation was indicated by the observation that some samples of pure freshly-distilled m-tolylhydrazine only gave a hydrazone/

hydrazone with great reluctance after several hours' heating. In addition, great difficulty was experienced in the preparation of acetophenone-methylphenylhydrazone — a substance obtained with great ease by Degen (Ann., 1886, 236, 154) on simply heating together for a short time acetophenone and asymmetric methyl-phenyl-hydrazine. Even on standing at room temperature, hydrazone formation was complete in twelve hours (Degen).

Using methylphenylhydrazine (supplied by British Drug Houses, Ltd.) freshly distilled, pure and water-clear, and the same acetophenone as was used for making the other hydrazones, little condensation took place after heating intermittently on the steam-bath for three days. The hydrazone was finally obtained by distilling the reactants in vacuo, when a 52% yield was obtained, together with a considerable amount of unchanged products (collected together as a separate fraction and amounting to 14% of the original material). The preparation of this hydrazone is described, not in this section of the thesis (Part I), but in Part III.

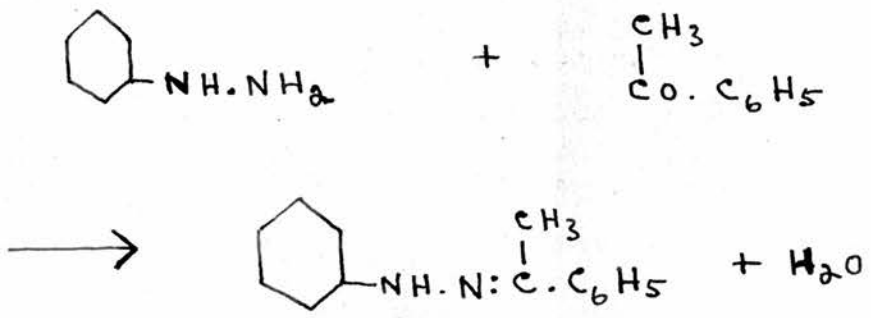
(1) Preparation of acetophenone-phenylhydrazone.

113 gms. phenylhydrazine.

126 gms. acetophenone.

The yield of hydrazone obtained was 199 gms., this/

this representing 90% of the theoretical. The substance crystallised from alcohol in white needles melting at 105°.



(2) Preparation of acetophenone-o-tolylhydrazone.

22 gms. ortho-tolylhydrazine.

22 gms. acetophenone.

These gave 32 gms. of hydrazone, melting at 101°. This yield represents 80% of the theoretical. The substance was previously unknown.

Nitrogen analysis (Ter Meulen):-

Found	N	12·5%
Calculated	N	12·5%

(3) Preparation of acetophenone-m-tolylhydrazone.

35 gms. meta-tolylhydrazine.

35 gms. acetophenone.

The hydrazone, after recrystallisation from alcohol, was isolated as long colourless prisms melting at 81°. The substance had not been made before, and was obtained in a yield of 59 gms., this representing 92% of the theoretical.

The/

The compound could be distilled in vacuo, when it came over at 214°-223° under 12 m.m. pressure, forming a thick viscid, yellow syrup which crystallised with extreme slowness to pure white prismatic needles, melting at 81°.

Nitrogen analysis (Ter Meulen):-

Found	N 12·4%
Calculated	N 12·5%

(4) Preparation of acetophenone-p-tolylhydrazone.

10 gms. para-tolylhydrazine.

10 gms. acetophenone.

The yield of hydrazone was 12·5 gms., or 67% of the theoretical. The substance crystallised from alcohol in colourless leaflets, melting at 125° as compared with the only previous quotation, 122° (Bovini, Centrallblatt, 1914 (1), 136).

(c) Preparation of Indoles.

Fusion of aryl hydrazones with zinc chloride at a high temperature.

All the fusions were carried out using zinc chloride, and no alternative catalyst was employed. The hydrazone was mixed in a nickel crucible with one to five times its weight of powdered anhydrous zinc chloride, and the crucible lowered into an oil or metal/

metal bath preheated to some definite temperature.

In this way, the time of exposure to a high temperature of the relatively labile hydrazone was reduced to a minimum. The mixture turned brown, and if a suitable fusion temperature had been chosen, the reaction took place within a few minutes. The molten mass suddenly frothed up vigorously but no ammonia was evolved. The crucible was lifted out of the bath immediately this occurred and allowed to cool, as the reaction completed itself almost at once (with cessation of the frothing). Further heating yielded no more indole, but led to charring of the bye-products of the reaction.

When the fusion mixture had cooled, the contents of the crucible were boiled with very dilute hydro-:chloric acid, and the aqueous extract decanted from the insoluble organic residue. The latter was then recrystallised repeatedly from alcohol until pure.

In consequence of the marked solubility of the indoles prepared in this research, heavy loss of material was sustained at each recrystallisation. In addition, several recrystallisations were necess-:ary to get rid of all impurities, especially as only a comparatively small amount of solvent was used each time.

In order to recover this loss in a useful form, all the rejected mother-liquors from successive recrystallisations were collected together, evaporated to dryness, and the residues dissolved in glacial acetic/

acetic acid. Powdered sodium nitrite was now added and the mixture shaken up. After a few minutes water was added and the yellowish-brown precipitate was filtered off, washed successively with water, alcohol and ether, dried and recrystallised two or three times from amyl acetate. In this way, practically the whole of the indole contained in the rejected mother-liquors was recovered as the iso-nitroso compound (see page 99).

(1) Preparation of 2-phenyl indole.

Fischer, Ann., 1886, 236, 116.

199 gms. acetophenone-phenylhydrazone.

626 gms. zinc chloride.

The fusion took place within 2-3 minutes at 190°, the yield of indole obtained being 76 gms. The filtrates from the recrystallisations of the indole gave 57 gms. of iso-nitroso compound, corresponding to 50 gms. of 2-phenyl indole. The total yield was thus 70% of the theoretical, although the yield of the pure indole itself (76 gms.) was only 42%. The substance melted sharply at 189°. (Fischer quotes 186°, but later observers quote 185°, 186°, 187° and 188°-189°. Bodforss, Ber., 1925, 58, 775, quotes 188°-189°).

A curious observation was made regarding this melting-point, namely, that it was not depressed at all by quite appreciable quantities of the impurities formed along with it in the fusion process. It was noted/

noted that a particularly pure sample, found in the form of a sublimate on one of cooled fusion products, had precisely the same melting-point as an evil smelling, dark coloured, and quite obviously impure specimen obtained by recrystallisation of the whole melt.

(2) Preparation of 2-phenyl-5-methyl indole.

19 gms. acetophenone-p-tolylhydrazone.
100 gms. zinc chloride.

At 175° the reaction took place in 1½ minutes, and 6 gms. of indole were isolated, melting at 216°. The filtrate gave 1½ gms. of iso-nitroso-compound. The total yield was thus 43%, but the yield of pure indole only 34% of the theoretical.

The melting-point quoted by Bischler (loc. cit.) was 213°.

(3) Preparation of 2-phenyl-6-methyl indole.

20 gms. acetophenone-m-tolylhydrazone.
100 gms. zinc chloride.

This indole had not been made before, and was remarkable for the exceptionally high fusion temperature required for its formation. The fusion did not succeed at 180°, 200° or 220°, and prolonged heating (more than half-an-hour) simply led to decomposition of the hydrazone and charring.

At 280° the reaction took place at once without charring, and after three recrystallisations of/

of the cooled residue from alcohol gave 7 gms. of indole as a first crop and a further 1 gm. as a second crop. This represented a yield of 44%, while the filtrates gave 9 gms. of iso-nitroso compound, equivalent to 8 gms. of indole. The total yield thus amounted to 87% of the theoretical.

The indole was obtained completely pure by these three recrystallisations and melted sharply at 193°.

Analysis:-

Found	C 86·9%	H 6·50%	N 6·76%
Calculated	C 86·9%	H 6·33%	N 6·76%

(4) Attempted preparation of 2-phenyl-7-methyl indole.

Acetophenone-o-tolylhydrazone was fused in 5 gm. lots with five times its weight of zinc chloride at various temperatures from 120°-400° but without success, no indole being isolated.

The hydrazone was prepared in exactly the same way as the isomeric compounds, which gave indole derivatives more or less readily. The same sample of zinc chloride was used as in the other cases, although a fresh sample of this substance was also tried, the same crucible and exactly the same method was employed, and various temperatures, but without success.

Fusions were carried out at 120°, 150°, 180°, 200°, 220°, 250°, 280°, 300°, 350°, and 400°, but in each/

each case profound decomposition took place with severe charring. The frothing characteristic of a successful fusion was observed to a slight extent in those carried out at 215° and at 350°, but neither in these cases nor in any of the others examined was any indole obtained.

In each case, the melt gave the pine-splint reaction to a slight extent at least, but the charring was so severe that isolation of the indole was quite impossible. Even an attempt to isolate the indole as the iso-nitroso compound - a procedure calculated to give an almost theoretical extraction of indole from any charred product (see page 100) - failed to reveal more than a trace of indole.

The severity of the charring with this hydrazone far exceeded that observed with the others, and it was concluded that, for some unknown reason, the conversion of this hydrazone into the desired indole could not be accomplished by this method.

Discussion of the Method.

The success of the fusions in the foregoing experiments appeared to depend chiefly on the choice of a suitable fusion temperature, this having to be found empirically by trial and error if the usual temperature (180°) was not found suitable for the particular hydrazone employed.

It was found, as a result of numerous attempts to/

to prepare α-phenyl-m-toluindole at different temperatures, that short exposure to a high temper-:ature succeeded where more prolonged exposure to a lower temperature failed to effect the synthesis, and only resulted in decomposition of the hydrazone and charring (see page 41).

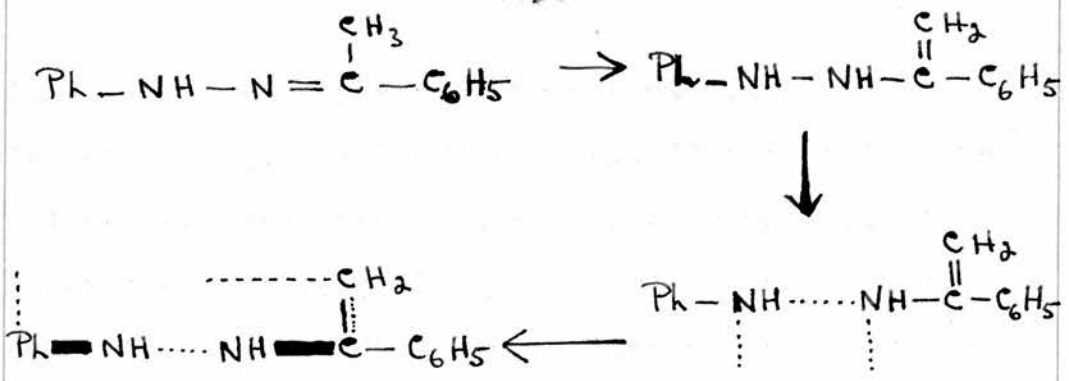
Regarding the relative ease of formation of the different indoles, the following notes may be made:-

Formation of α-phenyl-p-toluindole took place in 1½ minutes at 175°.

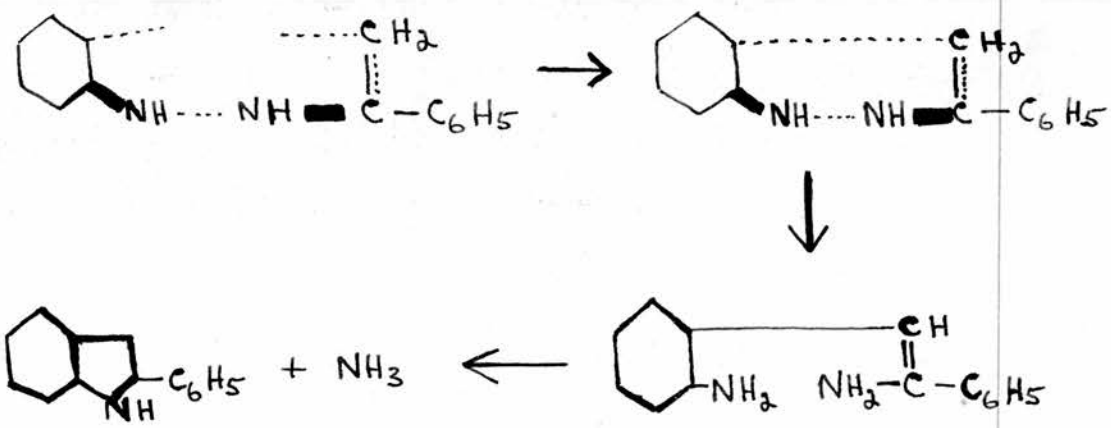
Formation of α-phenyl indole took 2-3 minutes at 190° (5-10 minutes at 180° according to Fischer). α-Phenyl-m-toluindole required a very high fusion temperature - 280°. α-Phenyl-o-toluindole could not be made by Fischer fusion at any temperature between 120° and 400°.

These differences can only be attributed to the different positions of the methyl group relative to the hydrazone grouping. The effect, however, cannot be a steric one of the type met with in "steric hindrance" or "restricted rotation". A more plausible explanation may be advanced as follows:-

If Robinson's mechanism of the Fischer synthesis is accepted as correct, it is seen that an essential step in the process is the development of a partial valency in some undefined position in the benzene ring portion of the hydrazone, (see page 142).



Only when this occurs in the ortho-position, however, can ring formation take place with production of an indole derivative.



It is conceivable, therefore, that the introduction of a methyl group may influence the ease with which this essential partial valency is developed, and in such a manner that this is made easier, more difficult, or almost completely inhibited, according as the group introduced occupies the para, meta or ortho positions.

On the other hand, the yields of the various indoles obtained were in inverse order to that which the above explanation would predict. It was observed/

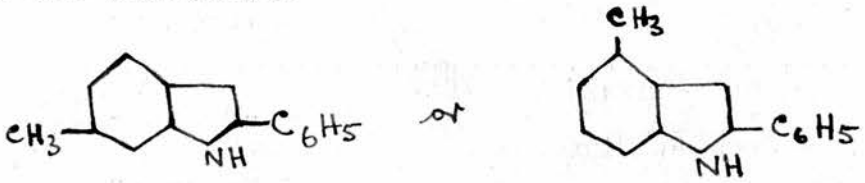
observed that the higher the fusion temperature required to effect the synthesis, the greater was the amount of indole formed. These points are summarised in the following table:-

Hydrazone used	Indole formed or expected	Fusion Temperature	Time Taken	Yield obtained
ortho	2-phenyl-7-methyl	-	-	nil
para	2-phenyl-5-methyl	175°	1½ mins.	43%
unsubsti-:tuted	2-phenyl	190°	2-3 mins.	70%
meta	2-phenyl-6-methyl	280°	½ min.	87%

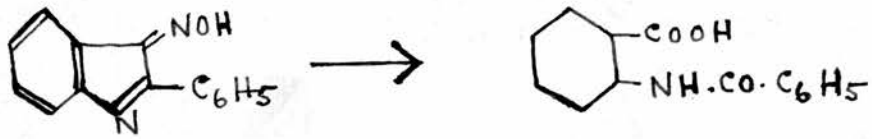
Considering the labile nature of the hydra-:zones, the increase in the yield of indole with elevation of the fusion temperature was most unexpected, and represented a most interesting and curious aspect of the reaction.

Attempt to orientate the methyl group in α-phenyl-m-toluindole.

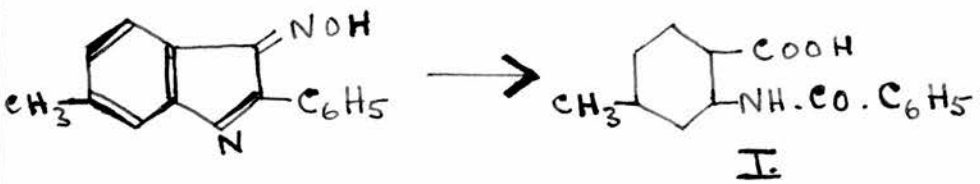
This substance, from its method of synthesis from m-tolylhydrazine (Fischer's method) or from m-toluidine (Bischler's method) must possess one of the two structures



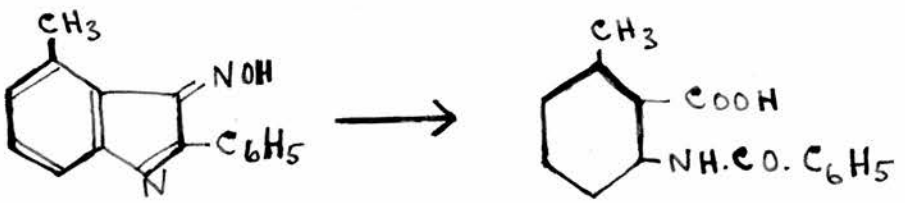
Now it has been shown by Angeli and Angelico (Gazz., 1900, 30 (2), 268,) that oxidation of the isonitroso-compound of α-phenyl indole by alkaline permangenate yields benzoylanthranilic acid.



It was therefore thought that oxidation of the isonitroso compound of α-phenyl-m-toluindole would yield a methyl benzoyl-anthranilic acid whose structure could be determined by comparing it with the known methyl benzoylanthranilic acids.



I.



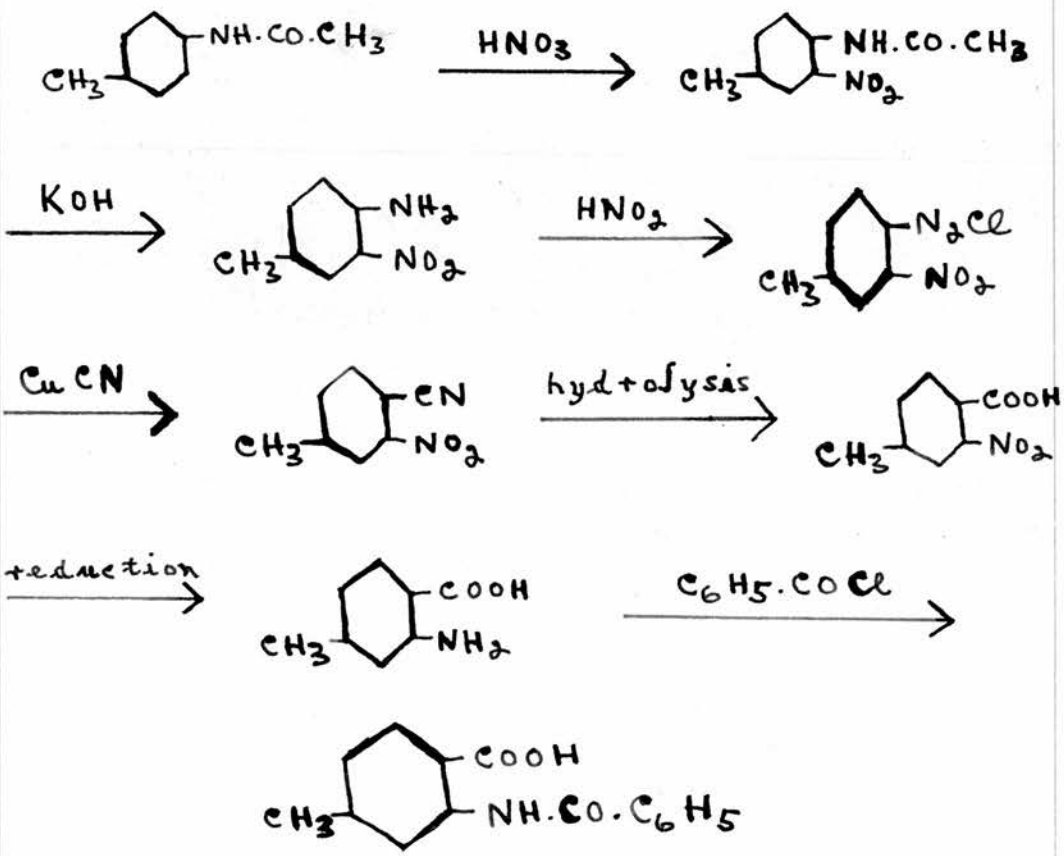
II.

These/

These substances (I and II) are not described in the literature and had to be synthesised.

Synthesis of 2-benzoylamino-4-methyl-benzoic acid.

This substance was prepared in the following stages:-



(1) Preparation of 2-nitro-4-methyl-aniline.

Noyes, Amer. Chem. Journal, 10, 475.

40 gms. para-acetotoluidide.

148 c.c. nitric acid (Sp.gr., 1·40)

59 c.c. sulphuric acid (Sp. gr., 1·84)

The/

The acids were mixed and the para-aceto-:toluidide added fairly rapidly, the mixture being vigorously stirred and placed in cold water so that the temperature remained between 30° and 40° during the addition. After standing for 15 minutes the mixture was poured into 700 c.c. water. The precipitate was filtered off, washed with water and well drained. It was then boiled with 90 c.c. of alcohol, and, when completely dissolved, a solution of 20 gms. potassium hydroxide in 25 c.c. water was added. The heating was continued for 15-20 minutes and the contents of the flask cooled rapidly. The precipitated nitro-toluidine was then filtered off and washed with 30% alcohol. Yield, 35 gms.

(2) Preparation of 2-nitro-4-methyl benzonitrile.

Noyes (loc. cit.)

The finely powdered nitrotoluidine (35 gms.) was placed in a flask with 1160 c.c. water. Sodium nitrite (20 gms.) and 60 c.c. of concentrated hydro-:chloric acid were added, and the mixture shaken vigorously for 10 minutes. The solution was then filtered, and the filtrate added as rapidly as possible to a solution of cuprous cyanide kept at 70°, taking care not to cool the solution too much. The nitrile separated as a yellowish-brown solid (or at a higher temperature as a less pure oil). When the reaction was complete, the solution was rapidly cooled and the nitrile filtered off at once. Yield, 34 gms.

(The/

(The solution of cuprous cyanide was prepared by adding 77 gms. potassium cyanide to a hot solution of 65 grams copper sulphate in 350 c.c. water.)

(3) Preparation of 2-nitro-4-methyl benzoic acid.

Noyes (loc. cit.)

This represented the most troublesome stage in the preparation of the 2-benzoylamino-4-methyl benzoic acid ultimately required, since the hydrolysis of the nitrile prepared above could only be carried out in 4 gm. lots - the yield of acid each time being about 1 gm..

2-Nitro-4-methyl-benzonitrile (4 gms.) was heated in a sealed tube with 50 c.c. of concentrated hydrochloric acid for 1-2 hours at 150°-160°. On cooling, the acid separated as long, thick, needles which were filtered off. The compound was purified by dissolving in dilute ammonia, filtering, and precipitating it from the filtrate by addition of hydrochloric acid. Finally it was recrystallised from hot water. Yield, about 1 gm..

(4) Preparation of 2-amino-4-methyl-benzoic acid.

The nitro-acid prepared as above (1 gm.) was added to an effervescing mixture of 3 gms. of tin and 4.5 c.c. of 25% hydrochloric acid. When the nitro-acid had completely dissolved, the tin was removed, the solution diluted with water and saturated with hydrogen sulphide. The resultant precipitate of stannous sulphide was filtered off, washed well with/

with water, and the combined filtrate and washings evaporated to small volume. On cooling, the acid chloride of the amino-acid separated as fine needles which were filtered off, washed with concentrated hydrochloric acid, dried, and warmed with the theoretical amount of very dilute ammonia. The resultant 2-amino-4-methyl-benzoic acid was obtained as a white, apparently amorphous, substance melting without decomposition at 177°.

Noyes quotes m.p. 177°-178° (decomposition).

(5) Preparation of 2-benzoylamino-4-methyl-benzoic acid.

Equimolecular quantities of benzoyl chloride and 2-amino-4-methyl-benzoic acid were dissolved separately in hot pyridine and the two solutions mixed. The mixture was brought to the boiling point and then allowed to cool. A white precipitate was thrown down, which was filtered off and recrystallised from alcohol. The substance was obtained in glistening white diamond shaped plates melting at 194°.

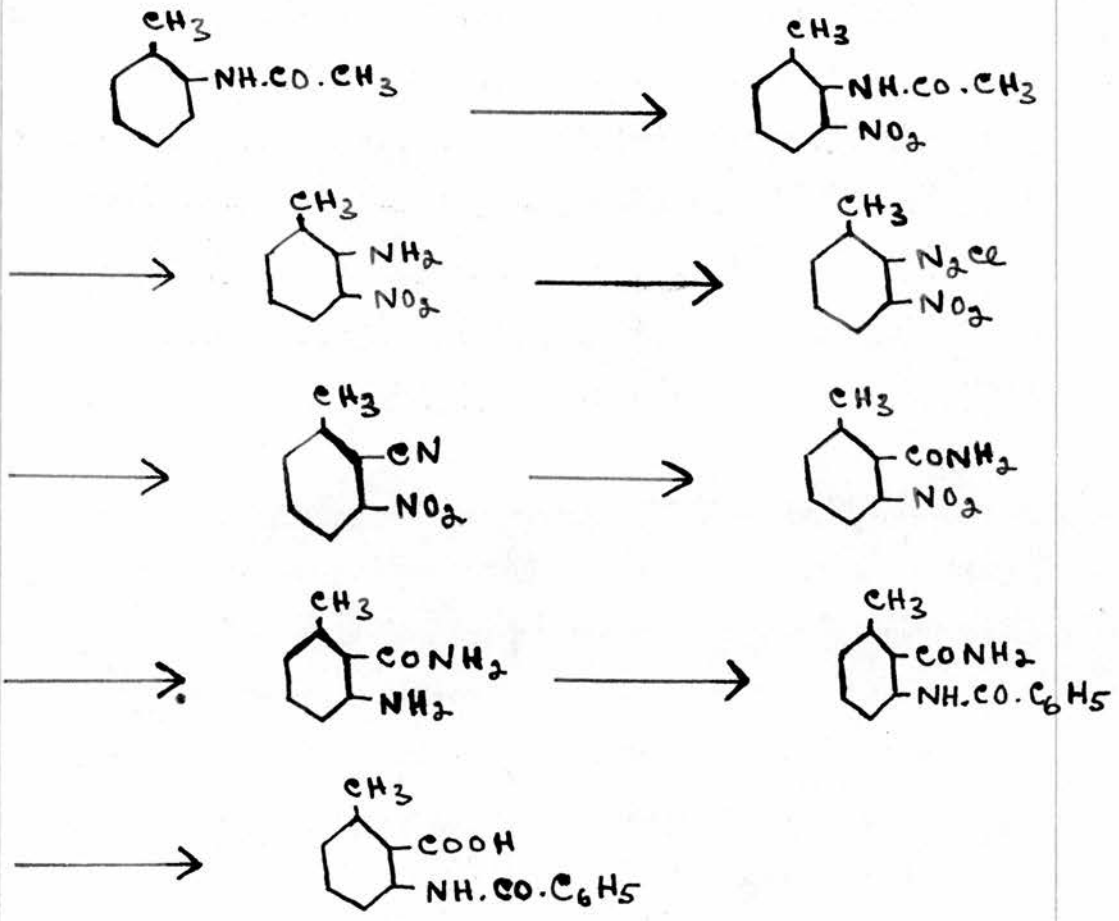
Nitrogen analysis:-

Found	5·45%
Calculated for $C_{15}H_{13}O_3N$	5·49%

Preparation/

Preparation of 6-methyl-2-benzoylamino-benzoic acid.

This was prepared in the following stages:-



(1) Preparation of 2-nitro-6-methyl aniline.

Ortho-acetotoluidide (80 gms.) was dissolved with heating in 56 c.c. acetic anhydride and 70 c.c. glacial acetic acid, the solution cooled in ice, and a mixture of 24 c.c. fuming nitric acid (sp. gr. 1·51) and 35 c.c. glacial acetic acid, slowly dropped in with stirring, the temperature being maintained between 15° and 20°. The mixture was stirred thoroughly and left overnight in the refrigerator, when it crystallised out. The crystal mush was stirred up with 600 c.c. of ice-water and filtered.

The/

The residue was then hydrolysed by boiling under reflux for two hours with 240 c.c. of 20% hydro-:chloric acid. Water (600 c.c.) was now added, the mixture cooled, and the dark-red precipitate filtered off.

Yield, 50 gms.

(2) Preparation of 2-nitro-6-methyl-benzonitrile.

Gabriel and Thieme, Ber., 1919, 52, 1081

2-Nitro-6-methyl aniline (30 gms.) was dissolved in 75 c.c. of glacial acetic acid, 36 c.c. of fuming hydrochloric acid added, and then, with cooling and vigorous shaking, 21 gms. of finely powdered sodium nitrite. Iced-water (300 c.c.) was now added and the mixture shaken vigorously. It was then filtered, and the filtrate poured in a fine stream into a solution of potassium cuprocyanide kept at 70°-80°.

(The potassium cuprocyanide solution was made by dissolving 72 gms. of copper sulphate and 78 gms. of potassium cyanide in 540 c.c. of water.)

An ochre-yellow precipitate appeared, which was filtered off and washed. It was then boiled under reflux for 1 hour with 240 c.c. of alcohol, and the mixture filtered hot. The nitrile was obtained as golden crystals on cooling the filtrate.

Yield obtained, 7·5 gms.

(3) Preparation of 2-nitro-6-methyl benzamide.

The above nitrile (7·5 gms.) was mixed with

31 c.c. of concentrated sulphuric acid and 15 c.c. of water, and the mixture heated to 140° with stirring. The nitrile all dissolved and the solution was allowed to cool to 115°-120° and kept at that temperature for 1½ hours. It was then diluted with 150 c.c. hot water.

On cooling, the amide was precipitated.

(4) Preparation of 2-amino-6-methyl benzamide.

The above nitro-amide (2 gms.) was dissolved in 10 c.c. concentrated ammonia (0·880), the solution made up to 14 c.c. with water, and a hot solution of 13 gms. ferrous sulphate crystals in 14 c.c. water added. The mixture was heated on the water-bath for one hour with frequent shaking, and was then cooled, filtered, and the black residue washed with water containing a little ammonia until a sample of the washings gave no cloudiness on acidification.

The combined filtrate and washings were concentrated by evaporation and made neutral to litmus by the addition of dilute hydrochloric acid. The solution was then cooled and extracted with ether. The ethereal solution was evaporated to dryness and the amino-amide obtained as a white sub-:stance melting about 105°.

(5) Preparation of 2-benzoylamino-6-methyl-benzamide.

Equimolecular quantities of benzoyl chloride

and/

and 2-amino-6-methyl benzamide were dissolved in hot pyridine, the mixture brought to the boiling point, and then allowed to cool. Woolly balls separated, and these were filtered off and recrystallised from alcohol.

The substance was obtained in white flakes melting at 161°-162°.

Nitrogen analysis:- (Micro-Dumas).

Found	11.2%
Calculated for $C_{15}H_{14}O_2N_2$	11.0%

(6) Preparation of 2-benzoylamino-6-methyl-benzoic acid.

The above amide was hydrolysed to the corresponding acid by boiling it with 8% sodium hydroxide until ammonia ceased to be evolved (½ hour). The solution was then cooled and the resultant precipitate filtered off. This was washed and dried, and found to melt at 246°-248°.

The filtrate was now acidified with dilute acetic acid, and the precipitate filtered off, washed and dried. It was found to melt at 248° either alone or mixed with the first product. The two substances were therefore the same. The substance burned completely with a smoky flame leaving no residue and was not a sodium salt. It was quite insoluble in water, hot or cold, but dissolved in hot dilute sodium hydroxide and hot dilute hydrochloric acid. It was recrystallised from benzene in fine needles melting/

melting at 248°.

Nitrogen analysis (Micro-Dumas):-

Found	5·45%
Calculated for $C_{15}H_{13}O_3N$	5·49%

Oxidation of 2-phenyl-3-isonitroso indole.

Angeli and Angelico, Gazz., 1900, 30 (2), 268.

1·5 gms. of 2-phenyl-3-isonitroso indole were dissolved, by prolonged boiling, in a mixture of 16 c.c. of 2N.sodium hydroxide and 65 c.c. of water. A hot solution of 3 gms. of potassium permanganate in 65 c.c. of water was now added gradually and the mixture boiled for one hour. The unchanged permanganate was destroyed by addition of sodium sulphite and the mixture filtered free from oxides of manganese. The residue was well washed with hot water and the combined filtrate and washings acidified with dilute sulphuric acid. A yellow precipitate appeared, which was filtered off and washed with water. Sodium carbonate solution was now poured over the filter paper containing the yellow residue, and the filtrate collected.

The filtrate was then acidified, when a precipitate of benzoylanthranilic acid separated. This was filtered off, washed, dried and recrystallised from alcohol. Observed m.p. 176°. M.p. after a second recrystallisation from alcohol, 179°-180°.

Mixed/

Mixed m.p. with benzoylanthranilic acid m.p. 180°, 179°-180°.

The residue, which consists of unchanged isonitroso compound and nitro-compound was extracted with alcohol, the alcohol evaporated to dryness and the residue recrystallised from aqueous alcohol. In this way was obtained

2-phenyl-3-nitro-indole

in gleaming pale yellow scales reflecting a sky-blue metallic lustre. M.p. 235°-236° (decomposition). Angeli and Angelico quote various melting-points from 237° to 241°. The substance has a very characteristic appearance corresponding exactly to the descriptions of Angeli and Angelico.

Oxidation of 2-phenyl-3-isonitroso-4 (or 6) - methyl indole.

This was carried out exactly as above.

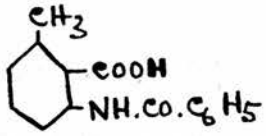
No nitro-compound was obtained, however, and the feebly acidic product of the oxidation consisted entirely of unchanged isonitroso compound.

Moreover, the strongly acidic product of the oxidation was found to be a yellow amorphous looking substance which, on recrystallisation from alcohol, was obtained in thinleaflets which decomposed without melting about 290°-294°.

This did not correspond with either of the

two/

two methyl-benzoylanthranilic acids expected:-

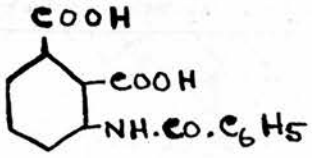


OR

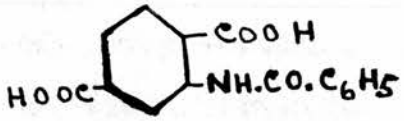
M.p. 248° M.p. 194°

The substance was acid to litmus and did not in the least resemble the nitro-compound.

It was, therefore, presumed, as a first assumption, that the methyl group of the indole had been oxidised to carboxyl with production of either



OR



The former substance has been prepared before and melts at 186°-187° (Kruber, Ber., 1929, 62, 2877). The latter substance is not described in the literature but the free amino-terephthalic acid is citron-yellow in colour and decomposes without melting at a high temperature. Its acetyl derivative also decomposes without melting.

Further evidence that the yellow product of the oxidation was a dicarboxylic acid was obtained as follows:-

A weighed quantity of the substance (0·067 gm.) was dissolved in 20·00 c.c. of 0·0458 N. sodium hydroxide. A yellow solution was obtained. This was titrated against 0·0420 N. hydrochloric acid using phenolphthalein as indicator. Owing to the yellow/

yellow colour of the original solution the neutral point was difficult to determine, but it was observed when 8·91 c.c. of acid (equivalent to 8·17 c.c. of alkali) had been added.

i.e. 0·0670 gs. of substance were equivalent to (20·00 - 8·17) c.c. or 11·83 c.c. of 0·0458 N. sodium hydroxide.

The equivalent weight of the substance is thus 124. Now the equivalent weight of methyl benzoylanthranilic acid is 255, while that of benzoylamino-terephthalic acid is 143.

The rather poor agreement between the observed equivalent weight (124) and that calculated for benzoylamino-terephthalic acid (143) is not surprising as the determination of the neutral point could not be performed at all accurately on account of the yellow colour of the solution.

The equivalent weight determination is, however, sufficiently accurate to demonstrate that the product of the oxidation is neither methyl-:benzoylanthranilic acid nor 2-phenyl-3-nitro-4(or 6)-methyl indole nor amino-terephthalic acid (equivalent weight 181).

That the substance does not contain any benzoic acid was shown by the ferric chloride test, no precipitation of ferric benzoate being observed.

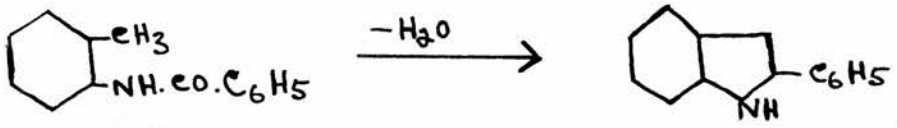
The subsequent synthesis of this α-phenyl-m-toluindole from p-xylidine by Madelung's method, and/

and its consequent formulation as the 6-methyl compound, supports the above assumptions, and suggests that the failure to orientate the indole by this method was probably due to the (unexpected) oxidation of the methyl group to carboxyl.

D. Preparation of Indoles by Madelung's Method.

Madelung, Ber., 1912, 45, 1131; D.R.P. 262327; Abstracts, 1914, (1), 89; Centralblatt, 1913, (2), 553, etc..

(1) Preparation of α-Phenyl Indole.



Sodium (3·4 gms.) was dissolved in about 100 c.c. of absolute alcohol contained in a 500 c.c. Pyrex bolt-head flask, fitted with a two-holed cork carrying two tubes fitted and bent as for a steam-distillation. The inlet tube led to the bottom of the flask, and was connected, via a sulphuric acid containing wash-bottle, to the coal-gas supply. The exit tube was attached to a downward leading condenser having a filter-flask fitted at its lower end as receiver. The side-tube of the filter-flask was connected by rubber tubing to the draught-hole so that all coal-gas bubbled through the reaction mixture was carried safely away.

Care was taken to avoid as far as possible contact of the sodium ethoxide solution with the air, since oxidation takes place readily with formation of brown and subsequently black products, which increase the difficulty of purifying the indole. Most of the alcohol was distilled off, benzoyl-o-toluidide (10 gms.) added, the air displaced again by/

by a stream of dried coal-gas, and the remaining alcohol distilled off. The residue was now heated on a saltpetre bath.

According to Mddelung, the temperature should be raised to 360°-380° and maintained there for a few minutes before allowing the reaction mixture to cool (in a stream of dry coal-gas). Copious frothing takes place and a solid yellowish-white residue is obtained, which, on heating to 360°-380° becomes light brown. When cold, the contents of the flask are treated with 300 c.c. of water and the mixture filtered, the insoluble portion, after thorough washing with water, being "recrystallised twice from alcohol, with addition of animal charcoal", "when the indole is obtained pure" in a yield 60% of the theoretical.

These instructions were carefully followed, all Madelung's observations were confirmed, but the product obtained was at once recognised from its appearance to consist chiefly of the starting product, benzoyl-o-toluidide, and not the indole sought. It was found, however, that the two substances were easily separable on account of the insolubility of the benzoyl-o-toluidide in ether. The mixture was therefore stirred with about 50 c.c. of cold ether and filtered. The residue, which gave neither the pine-splint reaction (page 90) nor Ehrlich's test (page 91), was dried (weight 5·0 g.) and identified

by/

by melting-point and mixed melting-point (143°) as benzoyl-o-toluidide. The filtrate was evaporated to dryness and recrystallised from alcohol, when 0·4 g. of pure α-phenyl indole (m.p. 189°) was obtained. The identity of the latter product was conclusively established by mixed melting-point and the pine-splint reaction.

The above yield (4·5% of the theoretical) compared very badly with Madelung's yield of 60%, but, though the preparation was repeated twice with longer heating, no greater yield was obtained. The method was also extended to the preparation of the Bz-methyl homologues of α-phenyl indole, but the same unsatisfactory result was attained. Attempts were therefore made to improve matters as follows.

Consideration of the process shows that the only real variables are (1) the temperature employed, and (2) the time of exposure to that temperature, neither of these, according to Madelung, requiring exact adjustment. It seemed therefore, that despite the latter's detailed description of the apparatus, with its "doppelt durchgebohrten Kork" which makes no provision for carrying an inside thermometer, the temperature measured should have been that within the flask. With this modification the following results were obtained.

After the whole of the liquid contents of the flask had been distilled off and the residue had set to a yellowish-white flaky crust, a condition corresponding/

corresponding to that of the previous experiments when the heating was stopped, the temperature was raised steadily and fairly rapidly. Thereafter, at a few points in the mass the mixture suddenly swelled out as a brown bubble and became liquid, some volatile material (alcohol or amine) being at the same time evolved. These bubbles appeared suddenly and independently, and gradually increased in number until the whole of the contents of the flask had been converted into a dark-brown frothing liquid. It was noticed that this stage was always reached just as the temperature recorded on the thermometer reached 360° (uncorrected).

It was thus impossible to pick out any intermediate stage in the reaction, and all that could be obtained was the yellowish-white product or the dark-brown one or a mixture of the two. Unfortunately, a certain amount of decomposition and charring always took place, and frequently this was so marked that isolation of the indole by recrystallisation became impossible, and resort had to be made to vacuum distillation. In those cases the reaction product, when cold, was treated with water and the insoluble portion distilled, under a pressure of about 0·5 m.m., in a simple, 1 c.m. wide, glass tube bent at right-angles in the middle and blown to a small bulb at one end. The latter served as distilling flask while the other limb formed both condenser/

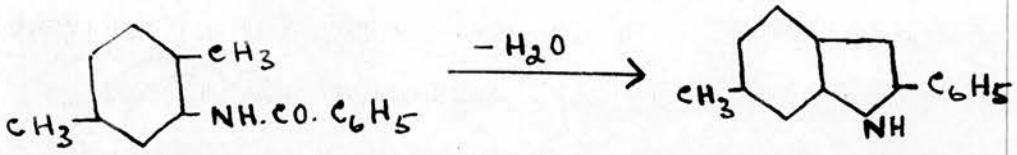
condenser and receiver. The apparatus, though simple, was very effective. The small quantity of indole obtained made the use of a Claisen flask impracticable, and the large amount of charred material present prevented the employment of Pregl's micro-vacuum-distillation apparatus. A further advantage of the bent tube was that if any severe bumping took place the whole of the contents of the condenser limb coulb be run back into the distillation flask without loss, so that the maximum yield of fairly clean distillate could always be obtained.

The indoles concerned (except 2-phenyl-4-methyl indole) distilled at undetermined temperatures as pale yellow oils, which solidified on cooling. These were recrystallised from alcohol. The yields obtained, however, were not much better than before, the only important advantage of the higher reaction temperature being that the starting materials, benzoyl-o-toluidide and the benzoyl-o-xylidines, were usually completely used up by conversion into indole or by decomposition, and were therefore absent from the final product. This was of great advantage in the preparation of at least one of the indoles (2-phenyl-5-methyl indole), where the separation of the latter from the original benzoyl-m-xylidine was not accomplished readily by any method tried (see page 73).

Generally, benzoyl-o-toluidide and the benzoyl-xylidines employed distilled in vacuo at about/

about the same temperature as the indoles made from them, and were usually soluble in the same solvents as the latter, so that separation of the two really resolved itself into an attempt to find a suitable solvent in which only one of the pair was sparingly soluble. Details of the individual preparations are recorded below.

(2) Preparation of 2-Phenyl-6-methyl Indole.



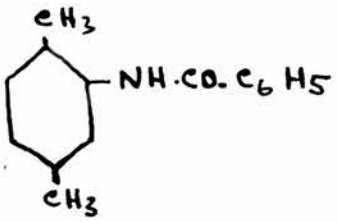
(a) Preparation of "pure" para-xylidine from the technical product.

Bornstein and Kleemann, D.R.P. 56322; Frdl., 3, 1001; C., 1891, 336.

The thick black tarry "technical" para-xylidine supplied by Hopkins and Williams was distilled, and the slightly red but clear clean distillate (b.p. 215°) saturated with sulphur dioxide. This precipitated, as addition compounds with the latter, all the isomeric xylidines except para-xylidine. These were removed by filtration, the filtrate heated on the steam-bath to remove sulphur dioxide, and then distilled.

(b)/

(b) Preparation of benzoyl-para-xylidine.



The above p-xylidine (71 gs.) was benzoylated by adding benzoyl chloride (83 gs.) in small quantities at a time, and grinding up the mixture in a mortar. The productwas filtered, the residue washed thoroughly with caustic soda then water, dried and recrystallised from alcohol, from which it separated as white needles melting at 150°. The melting-point did not change on further recrystallisation.

The yield obtained was 23 gs., representing 18% of the theoretical.

The melting-point quoted in the literature is 140° (Pflug, Ann., 1889, 255, 169; Hübner, Ann., 1881, 208, 322), but these authors only obtained the product melting at 140° after repeated recrystallis-:ations from alcohol - a certain indication that it was contaminated with isomers. In addition, both papers are old, and neither of them gives any information as to how the p-xylidine was prepared or purified. On the other hand, a comparative study of the melting-points of its isomers leaves no doubt about the constitution of the benzoyl-xylidine, melting-point 150°, obtained above.

(c)/

(c) Preparation of 2-phenyl-6-methyl indole.

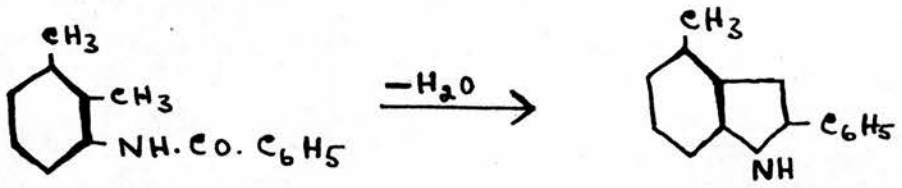
This was prepared in exactly the same way as 2-phenyl indole (page 61), 10 g. of benzoyl-p-xylidine being used, and the temperature measured being that of the heating bath (360°). The mixture of 2-phenyl-6-methyl indole and benzoyl-p-xylidine obtained was separated by boiling with ligroïn and filtering hot. From the filtrate was recovered 4 g. of the latter compound, while the residue, after two recrystallisations from alcohol gave 0·29 g. of indole melting sharply at 192·5°. (Yield, 3·5% of the theoretical).

The substance, therefore, was identified with the α-phenyl-m-toluindole (m.p. 192·5°) made by the methods of Fischer and Bischler, a conclusion which was confirmed by a mixed melting-point determination (192·5°). In addition, the indole was converted into the isonitroso-compound (page 99), and the latter, after purification, found to melt with decomposition at 238° either alone or mixed with an approximately equal quantity of isonitroso-α-phenyl-m-toluindole.

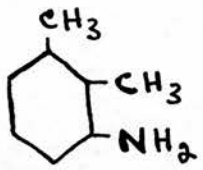
In this way, therefore, α-phenyl-m-toluindole was shown to be the 6-methyl derivative and not the 4-methyl compound. (See pages 23 and 41.)

(3)/

(3) Preparation of 2-Phenyl-4-methyl Indole.

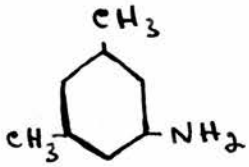


(a) Attempted separation of 3-amino-o-xylene from "technical o-xylidine".

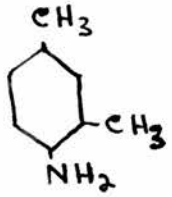


The preparation of this substance in a sufficient degree of purity (i.e. containing not more than 10% - 15% of its isomers), presented a difficult problem, and threw considerable doubt on the methods recommended for its isolation. For this reason the subject will be discussed in some detail.

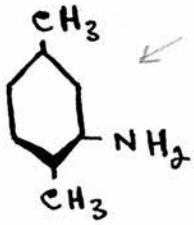
Commercial xylidine is prepared by nitration and reduction of coal-tar xylene containing all three isomers, and contains all the isomeric xylidines except the symmetrical compound (I.).



I.



II.



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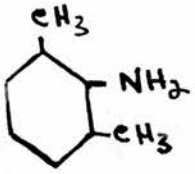

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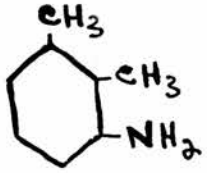

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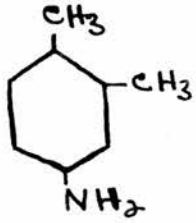


VI.

For the separation of these five substances two methods are available - that of Hodgkinson and Limpach (J.C.S., 1900, 77, 65) and that of Morgan and Hickinbottom, (J.S.C.I., 1926, 222). The former appeared to be the more suitable for the preparation of the 3-amino-o-xylene (V.) required, and was therefore applied to the "technical o-xylidine" supplied by Messrs. Hopkins and Williams.

This substance was distilled (b.p. 220°-222°), mixed with one quarter of its weight of glacial acetic acid and set aside for 48 hours. No precipitate appeared during that time, so the mixture was assumed to be free from 4-amino-m-xylene (II.), the precipitation of which as the acetate commences at once and is complete in 24 hours, according to Hodgkinson and Limpach.

Excess concentrated hydrochloric acid was now added and the mixture cooled, but as no precipitate of/

of p-xylidine (III.) hydrochloride appeared, the absence of this isomer was assumed. The whole was then distilled in a retort until the temperature of the liquid reached 250°. Hydrochloric and acetic acids distilled off first, followed by a mere trace of 2-amino-m-xylene (IV.) hydrochloride as a sublimate. The black residue in the flask was therefore not treated further for the recovery of the two remaining isomers, 3-amino-o-xylene (V.) and 4-amino-o-xylene (VI.), since these were apparently the only ones present in the starting material.

A fresh portion of the latter was therefore boiled for three hours with excess of 25% formic acid and the product poured into water, when a brown oil was obtained. This showed no signs of solidifying for ten days, after which surface crystallisation commenced, but proceeded so slowly that only a small fraction had crystallised after several months. Hodgkinson and Limpach claim to have separated the two isomers by taking advantage of the different rates of crystallisation of the two formyl derivatives from this oil, a claim which is discussed below (page 82). Even admitting the claim, however, the method is obviously far from satisfactory, and was abandoned as unnecessary in the present work, since only the 3-amino compound (V.) could give rise to an indole derivative by Madelung's process. The mixture was therefore benzoylated/

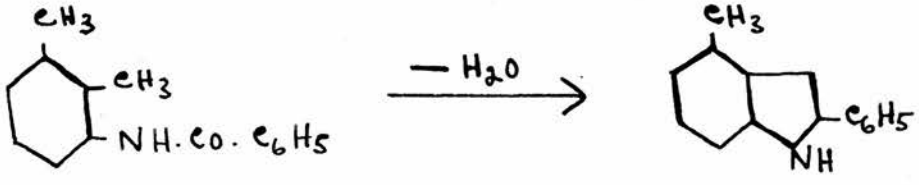
benzoylated and the product heated to 360° with sodium ethoxide, when an indole derivative was obtained.

(b) Benzoylation of "technical" o-xylidine.

Freshly distilled xylidine (15 g.) was benzoylated as described above for the para compound, when the benzoyl derivative was obtained as glistening white needles melting at 143°-153°, the yield being 16·5 g., or 60% of the theoretical. The substance was very soluble in ether, chloroform, benzene, carbon disulphide, glacial acetic acid, acetone, alcohol (hot) and ligroïn (hot). After nine recrystallisations from alcohol a constant melting-point of 192° was obtained.

This melting-point at once aroused suspicions, since 4-benzoylamino-m-xylene (II.) was known to melt at 192°, while the benzoyl derivatives of 3-amino-o-xylene (V.) and 4-amino-o-xylene (VI.) are both unknown.

(c) Attempted preparation of 2-phenyl-4-methyl indole.



The benzoyl-xylidine obtained above (10 g.) was heated to 360° with sodium ethoxide (10 g.) in the manner described above for α-phenyl indole, the temperature/

temperature measured being that of the heating-bath. The cooled product, after extraction with water and recrystallisation from alcohol, was obtained as a light brown substance melting at 128°-142°, and weighing 4 g..

Separation of the indole from benzoyl-xylidine was not accomplished so readily as in the previous two cases as the two substances appeared to be about equally soluble in all the common solvents. Eventually the mixture was placed in a Sohxlet thimble fitted into the neck of a conical flask, and boiling petrol ether (b.p. 60°-80°) poured over it.

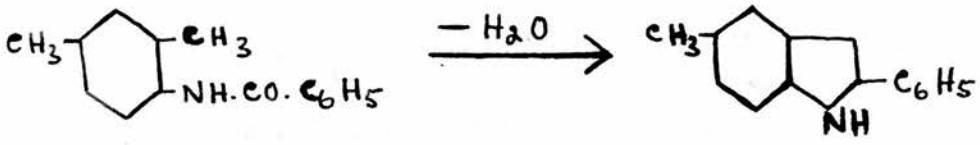
The residue (3·7 g.) now melted at 152°-161° either alone or mixed with an approximately equal quantity of benzoyl-xylidine (m.p. 152°-162°), and was therefore unchanged starting material. It did not give either the pine-splint reaction or Ehrlich's test. The filtrate, on evaporation, deposited a white crystalline substance (0·27 g.) melting at 156°-172° and giving a strong pine-splint reaction.

Since the purification of such a small quantity of very impure indole was considered impracticable, it was converted, for identification, into the isonitroso-compound (page 99). The latter substance after two recrystallisations from amyl acetate, was obtained in a yield of 0·21 g., and melted at 261°(d.). A mixed melting-point determination with 3-isonitroso-2-phenyl-5-methyl indole (m.p. 273°(d.)) gave 268°(d.).

The/

The isonitroso-compound was next benzoylated (page 107) and the product recrystallised three times from benzene when the constant melting-point 159° was obtained. This was not depressed by admixture with 2-phenyl-3-benzoyloximo-5-methyl indolone (m.p. 159°-160°), so that it was now evident that the original indole must have been 2-phenyl-5-methyl indole and not the 4-methyl compound, the low melting-points of the indole and isonitroso-compound being probably explained by the presence of isomers.

It therefore appeared that the xylidine separation process had failed, and that, instead of being a mixture of the two ortho-xylidines, the "technical ortho-xylidine" supplied by Messrs. Hopkins and Williams was chiefly 4-amino-m-xylene.



Inorder to make certain that the separation process had been carried out correctly, the latter was repeated twice, but with the same result. No separation of 4-amino-m- xylene acetate took place even after 72 hours. The substance was therefore benzoylated as before, and the product submitted to Madelung's process. This time the reaction mixture itself was heated to 360°, the temperature being recorded by a thermometer fitted inside the flask. The substance obtained, after three recrystallisations from/

from alcohol, melted at 203°-206°, the yield being 0·040 g. As the indole diminished rapidly in quantity at each recrystallisation further purification became impracticable. A mixed melting-point determination was therefore made with 2-phenyl-5-methyl indole (m.p. 216°), when the figure 211° was observed.

Further, the whole of the indole obtained, including that in the recrystallisation mother-liquors, was converted into the isonitroso-compound (page 99). The yield obtained was 0·93 g., the substance melting with decomposition at 261° and 263·5° after the first and second recrystallisations from amyl acetate. Admixture with 2-phenyl-3-isonitroso-5-methyl indolone (m.p. 273° (d.)) raised the melting-point to 268° (d.). On acetylation, (page 110) the compound gave a derivative which melted at 164° after four recrystallisations from ligroïn, the latter melting-point being raised to 166° on addition of 2-phenyl-3-acetyloximo-5-methyl indolone (m.p. 170°).

There was therefore no doubt that the indole prepared was mainly the 5-methyl derivative, heavily contaminated, however, with at least one isomer.

A fresh lot of "technical ortho-xylidine" was then obtained from British Drug Houses, Ltd.. This was distilled and benzoylated as before, the product being submitted to the Madelung synthesis.

The/

The xylidine distilled at 213°-220°, mostly at 213°-215° - a suspicious feature, since the two ortho-xylidines boil at 221°-226° while all the other isomers boil at ~~221°-226°~~ 211°-216°. The benzoyl derivative was obtained in a yield of 65% of the theoretical. The indole was prepared by the use of an inside temperature of 360°, and was isolated by distillation in vacuo (b.p. 210°-250° at 0·4 m.m. pressure). Recrystallisation of the distillate from alcohol gave 0·60 g. of indole melting at 201°-205°. The yield was thus 7% of the theoretical, while, after a second recrystallisation, the substance melted at 210° when alone and at 214° when mixed with 2-phenyl-5-methyl indole (m.p. 216°). It was evident, therefore, that this "technical ortho-xylidine" also consisted chiefly of 4-amino-m-xylene. It was therefore submitted to part of the separation process of Hodgkinson and Limpach, with the following results.

(d) Examination of B.D.H. technical ortho-xylidine.

Freshly distilled xylidine (202 g., b.p. 213°-220°) was mixed with glacial acetic acid (50 g.) and set aside. Only after three and a half days did a precipitate appear. After a further 12 hours, this was filtered off, when a filtrate amounting to 192 g. was obtained, the residue of pressed xylidine acetate weighing 56 g.. This represented the removal, as acetate, of 40 g. of xylidine or 20% of the substance started with.

To/

To the filtrate obtained above was added 18 g. of concentrated hydrochloric acid, but no separation of p-xylidine hydrochloride took place. On cooling in a freezing mixture a few crystals separated, but these went into solution again at room temperature and were not therefore the precipitate sought. The mixture was left standing for 24 hours, but without result.

The free bases were now recovered by neutralising with sodium carbonate, extracting with ether and distilling the extract, after evaporation of the ether.

The xylidine (131 g.) was benzoylated as before, using 153 g. of benzoyl chloride, the yield obtained being 150 g., or 62% of the theoretical. The benzoyl derivative (10 g.) was then submitted to the Madelung synthesis, and the indole isolated by distillation in vacuo. The product obtained was recrystallised three times from alcohol, the melting-points observed after each recrystallisation being respectively 180°-182°, 196°-200° and 206°. A mixed melting-point determination with 2-phenyl-5-methyl indole (m.p. 216°) gave 210°-211·5°, so that it was at once apparent that the indole obtained was still the impure 5-methyl compound and not the 4-methyl isomer desired.

Since, therefore, "technical ortho-xylidine" still consisted chiefly of 4-amino-m-xylene even after removal of 20% as acetate, it appeared that the original/

original substance must have contained at least 60% - 70% of this isomer. The matter was therefore taken up with the manufacturers, British Drug Houses, Ltd., but without result, the latter claiming that their analysis showed that the product supplied contained 82·4% of 4-amino-o-xylidine, which, incidentally, is not the isomer required for the synthesis under investigation.

The B.D.H. method of analysing technical o-xylidine is to submit it to a separation process substantially based on those of Hodgkinson and Limpach and of Morgan and Hickinbottom (loc. cit.). 4-Amino-m-xylene was separated as acetate and p-xylidine as hydrochloride, and it is stated that these substances were only obtained in small amount. The residue was then converted into the picrate by the method of Morgan and Hickinbottom, when a yield was obtained equivalent to 82·4% of "4-amino-o-xylene". The product, however, melted at 210° (B.D.H. determination), from which the firm conclude that the picrate obtained was that of 4-amino-o-xylene (m.p. 220° — Morgan and Hickinbottom), although the picrate of 4-amino-m-xylene is recorded as melting at 209° (Beilstein).

In view of these facts it was considered useless to persist in the attempts to prepare 3-amino-o-xylene from "technical ortho-xylidine".

Discussion of the xylidine separation processes.

As it is readily understandable that the separation of the five isomers present in commercial xylidine must necessarily present a difficult problem, it is not surprising to find many inconsistencies and contradictions in the two methods employed for the purpose.

In both the first step is exactly the same - separation of the 4-amino-m-xylene as acetate by addition of 1 g. of glacial acetic acid for every 4 g. of xylidines started with. This separation is not by any means complete, a fact which Hodgkinson and Limpach (1900) did not appear to realise, since they have given the following figures for the percentages of the different isomers present, based on their own separations:-

4-amino-m-xylene	40 - 42%
p-xylidine	30%
2-amino-m-xylene	2·7%
3-amino-o-xylene	9 - 11%
4-amino-o-xylene	15%
approximate total	99%

Morgan and Hickinbottom (1926) admit the incompleteness of the separation, and state that even if pure 4-amino-m-xylene is treated according to their process, only 60% is precipitated as acetate. If this is so, then the figures of the earlier authors must be erroneous, and about 48% of the material/

material left after the acetate separation, and described as consisting of the last four isomers on the above list, must be 4-amino-m-xylene.

Again in both processes the next step is the separation of the p-xylidine as the hydrochloride, the only difference being that whereas the earlier authors carry out the precipitation in presence of the acetic acid left over from the first separation, the later workers first recover the free bases and then treat these with concentrated hydrochloric acid. Commercially, the residue from these two separations is apparently sold without further purification as "technical ortho-xylidine", and, according to Hodgkinson and Limpach, should contain about 10% of 2-amino-m-xylene, 35% of 3-amino-o-xylene and 55% of 4-amino-o-xylene. Obviously this cannot be the case, and since, even after removal of 20% as the acetate, the mixture still gives 2-phenyl-5-methyl indole by the Madelung synthesis, it is apparent that a very large proportion of 4-amino-m-xylene must be present.

Now the p-xylidine hydrochloride fraction (30% of the whole) is admitted by Morgan and Hickinbottom to be very impure, but it must consist chiefly of the isomeride stated, since it is used after only one recrystallisation for the preparation of pseudo-cumidine. If, therefore, it is assumed that in the separation of 4-amino-m-xylene as acetate only 60% of this isomer is removed, it follows that "technical/

"technical ortho-xylidine" contains at least 60%-70% of 4-amino-m-xylene, in agreement with the conclusions reached as a result of the attempts to prepare 2-phenyl-4-methyl indole (pages 69 to 77).

This conclusion is supported by two further facts. Firstly, B.D.H. "technical ortho-xylidine" distilled at 213° to 220°, three-quarters of it at 213°-215°, whereas the two ortho-xylidines boil at 221°-223·5° and 223°-226° respectively, and 4-amino-m-xylene at 212°-216°. (The range of boiling-points quoted in the last three cases are given so as to embrace all the quotations given in Beilstein for the compounds referred to.) Secondly, the analyses found for commercial xylene in the literature (unfortunately no recent determinations are available) give an m-xylene content of at least 55%, the usual figure being 86% (Levinstein, J.S.C.I., 1884, 3,77). In view of this fact, we may justifiably expect the total m-xylidine content of commercial xylidine to be at least 55% and nearer 86%, instead of less than 45% as quoted by Hodgkinson and Limpach.

Further, Morgan and Hickinbottom, using a sample of xylidine from which the para and meta isomers had been partially removed, found that the acetate separation, which they themselves state to be only 60% effective, removed from their starting material a weight of 4-amino-m-xylene equivalent to 33% of the total. It is apparent, therefore, that even after the first partial separation of this substance/

substance by the manufacturers, the xylidine they used still contained about 55% of 4-amino-m-xylene.

If Hodgkinson and Limpach's evidence for having obtained 3-amino-o-xylene from commercial xylidine (in a 10% yield) is examined, it is at once seen to be dubious.

Their case is based solely on the melting-point of the acetyl derivative, given as 132°. Since, however, the acetyl derivative of 4-amino-m-xylene is given various melting-points from 127° to 130° while 3-acetylamino-o-xylene is listed with melting-points 131° and 134°, this evidence can scarcely be accepted as being of much value.

It is noteworthy that Morgan and Hickinbottom (1926) make no claim to have isolated 3-amino-o-xylene from commercial xylidine, the reader being left to infer that the residue which has escaped precipitation in the processes described for the separation of 4-amino-m-xylene, p-xylidine and 4-amino-o-xylene, and which amounts to 25% of the whole, will contain all of the 3-amino-o-xylene present in the original xylidine, in admixture with such quantities of the other isomers as have escaped the above precipitations. Actually, since an amount of 4-amino-m-xylene equivalent to 22% of the original material has been shown to have escaped the acetate separation, it appears that the 25% residue must consist largely of this compound.

Finally,/

Finally, the percentage of 4-amino-o-xylene in commercial xylidine is estimated by Morgan and Hickinbottom to be 4% - 7%, as compared the figure 15% given by Hodgkinson and Limpach, this discrepancy being probably accounted for by the presence of a considerable amount of 4-amino-m-xylene in the product obtained by the latter authors.

Reviewing the whole of the above evidence, therefore, it is the considered opinion of the present author that the separation of even approximately pure 3-amino-o-xylene from technical xylidine cannot be accomplished by the accepted methods, since the process used for the separation of the main constituent, 4-amino-m-xylene, is quite inadequate. Secondly, it is now maintained that the fraction of commercial xylidine described by Hodgkinson and Limpach as 3-amino-o-xylene is really 4-amino-m-xylene.

Experiments were carried out on freshly-distilled "technical o-xylidine", variously proportioned mixtures of this substance with glacial acetic acid being set aside to crystallise. It was found that the amount of precipitate formed increased with the proportion of acetic acid, until the amount of the latter reached about 25% of the weight of xylidine, further increase in this proportion being accompanied/

accompanied by a progressive reduction in the quantity of precipitate obtained. Furthermore, it was found that the precipitation of the acetate ceased when about one third of the acetic acid added had separated in the form of this compound, so that the solution always contained a considerable amount of both 4-amino-m-xylene and acetic acid. The statement of Hodgkinson and Limpach, that an almost quantitative separation of 4-amino-m-xylene may be effected by the addition of the theoretical quantity of acetic acid, was therefore not substantiated. This discrepancy, of course, is partly accounted for by the fact that the material used in this research had already been partially separated, while the latter authors used unseparated material. In the opinion of the present writer, however, this observation merely strengthens the view that Hodgkinson and Limpach were mistaken in their belief that they had effected a fairly complete separation of 4-amino-m-xylene.

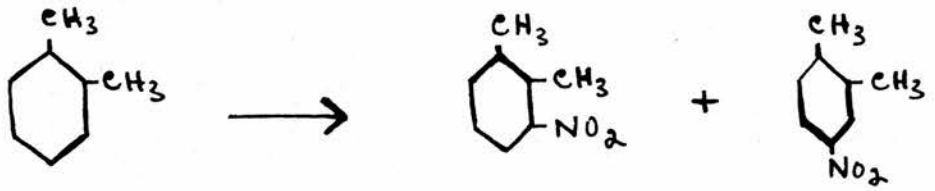
Preparation of 3-amino-o-xylene from o-xylene.

The only other way of obtaining 3-amino-o-xylene except from the technical product discussed above is by nitration and reduction of ortho-xylene, and all data recorded in Beilstein regarding this amine appear to have been collected by authors who employed this method.

Nitration/

Nitration of o-xylene.

Crossley and Renouf, J.C.S., 1909, 95, 216.



50 g. o-xylene.

50 g. fuming nitric acid

100 g. concentrated sulphuric acid.

The xylene was cooled in a freezing-mixture and stirred vigorously with a mechanical stirrer, while the acid mixture, also cooled below 0°, was added drop by drop, keeping the temperature below 0°. At first the addition of acid required to be made very slowly, while the nitration mixture became very dark. Subsequently, however, the acid could be added more rapidly, while the colour became much lighter.

The reaction mixture was poured into water and extracted with ether, the ether solution washed with caustic soda solution, then with water and dried over calcium chloride. After removal of the ether, the mixture of nitro-compounds was distilled in vacuo, the distillate being collected until it began to solidify in the condenser (b.p. 150°-190° at 36 m.m. pressure).

In this way, the two mono-nitro-o-xylenes were obtained, free from the dinitro-compounds, and containing/

containing eight times as much 3-nitro-o-xylene as 4-nitro-o-xylene. (Crossley and Renouf).

The yield obtained was 62 g., representing 87% of the theoretical.

The separation of the two isomers can only be effected by a long tedious series of fractional distillations, fractional freezings and extractions, which, while involving heavy loss of material, fail to give a complete separation. This purification, however, was quite unnecessary, as only the 3-nitro-compound could give an indole derivative on reduction, benzoylation and submission of the benzoyl derivative to the Madelung synthesis.

The separation was not therefore attempted.

Reduction of nitro-o-xylene.

Noelting and Forel (Ber., 1885, 18, 2671) performed this reduction with iron filings and acetic acid, but give no other instructions.

113 g. nitro-o-xylene.
400 c.c. glacial acetic acid.
400 c.c. water
190 g. iron filings.

The acid, water and nitro-o-xylene were mixed and shaken in a large flask. The iron filings were added gradually in very small quantities at a time, with shaking and strong cooling. The reaction

was/

was very vigorous, especially at the beginning, and tended to get out of hand unless great care was taken to add the iron slowly and keep the mixture well cooled.

After completion of the reaction, the mixture was filtered and the filtrate made alkaline with sodium hydroxide and steam-distilled. The distillate was extracted with ether, the ether extract dried over sodium hydroxide, and the ether evaporated. The residue was distilled, when 46 g. of xylidine were obtained, boiling at 219°-225°. This boiling-point was very satisfactory, while the yield amounted to 43% of the theoretical.

Benzoylation of o-xylidine.

46 g. o-xylidine

54 g. benzoyl chloride.

The xylidine was suspended in dilute caustic soda solution and the benzoyl chloride added gradually with shaking and cooling. The mixture was ground in a mortar, filtered, the residue washed with caustic soda, then water, and finally recrystallised from alcohol. The product formed glistening white needles melting at 164°-166°, but after three more recrystallisations was still impure and melted at 179°-180°. The attempts to get rid of the 4-benzoylamino-o-xylene by this means were therefore abandoned.

The yield of benzoyl-o-xylidine after the first/

first recrystallisation was 57 g., or 73% of the theoretical.

Preparation of 2-phenyl-4-methyl indole.

The mixed benzoyl-o-xylidines (10 g.) were heated in absence of air with sodium ethoxide (10 g.) in accordance with the method previously described. Severe charring took place, however, when the temperature was raised to 360° inside the reaction vessel, and the product obtained, by distillation in vacuo, was a brown decomposed oil which did not solidify or give the pine-splint reaction.

The synthesis was therefore repeated several times to ascertain the best conditions for obtaining the indole. It was found that the appearance of the mixture was a much more reliable guide than the temperature, and that the heating was best stopped when the contents of the flask became dark brown, and before they began to bubble and melt. This occurred at various temperatures between 290° and 320°.

In each case the product obtained, whether isolated by recrystallisation from alcohol or by distillation in vacuo, still consisted chiefly of unchanged benzoyl-o-xylidine, and, after three recrystallisations from alcohol, failed to give the pine-splint reaction, all the indole present having passed into the mother liquors.

The isolation of the indole itself was not, therefore/

therefore, accomplished, this being due to the comparatively small yield and the difficulty of separating it from unchanged reactant.

The alcoholic mother-liquors from the above were therefore mixed with glacial acetic acid and treated with a cold concentrated aqueous solution of sodium nitrite. On pouring the product into water, a yellow precipitate was obtained, which, after filtering off, washing with alcohol and ether, and recrystallising twice from amyl acetate, was found to melt with decomposition at 251°. The yield obtained was 0·49 g. equivalent to 5·5% of the theoretical. Further recrystallisation from amyl acetate did not raise the melting-point, so that the substance was concluded to be

2-phenyl-3-isonitroso-4-methyl indole.

Nitrogen Analysis:- (Micro-Dumas method)

Found	N	11·8%
Calculated	N	11·9%

The substance possessed the same characteristic properties as its isomers.

In order to make quite certain that the compound obtained really was the new isomeride and not one of those already known, it was (a) benzoylated and (b) acetylated, and the resultant derivatives shown by their melting-points to be new. These compounds are described together with their isomers on pages 110 and 113.

General properties of α-phenyl indole and its Bz-methyl homologues:-

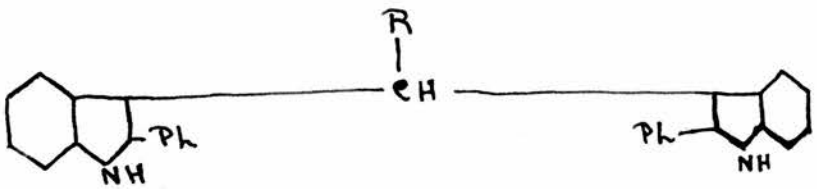
These are white crystalline substances, stable in air and at high temperatures. They give sharp melting-points, without decomposition, and can be distilled in vacuo (b.p. about 250° at 10 m.m. pressure). Their solutions show a blue, violet or purple fluorescence. They are insoluble in water or petrol ether, but readily soluble in alcohol, ether, chloroform, carbon disulphide, acetone, glacial acetic acid and benzene.

All these indoles impart an intense purple colour to a pine-splint dipped into an alcoholic solution of the indole and then into concentrated hydrochloric acid (pine-splint test).

(The purple colour produced here is characteristic of the phenyl indoles; the methyl indoles give a cherry red colour and the dihydro-indoles give an orange colour.)

The phenyl indoles are odourless and involatile in steam, and like most other indoles they form addition compounds with picric acid, trinitrobenzene, etc.

The 3-position is very reactive and the indoles yield 3-iso-nitroso compounds with nitrous acid, and condensation compounds with aldehydes, of the general form.



This latter reaction forms the basis of Ehrlich's test for indoles, the aldehyde employed being p-dimethylamino-benzaldehyde. Ehrlich's reagent is prepared by dissolving 1 gram of this aldehyde in 20 c.c. of concentrated hydrochloric acid and adding 119 c.c. of alcohol. The resultant solution, on addition of a mere trace of α-phenyl indole or any of its Bz-methyl homologues gives a reddish-violet colouration in the cold, which becomes purple on heating. The test is a very delicate one.

Unlike indole itself and its methyl homologues, the phenyl indoles are not polymerised by the action of strong acids. They dissolve, however, in concentrated sulphuric acid and are precipitated unchanged on addition of water.

E. Preparation of Derivatives of the Indoles.

Although a large number of substances derived from α-phenyl indole have been prepared, only three derivatives of its Bz-methyl homologues are so far known. These were prepared with the object of characterising the parent compounds, but their use-:lessness for this purpose is shown by the following table of melting-points.

Indole/

Indole	Picrate	"Nitroso-compound"	Benzylidene compound
α-phenyl indole	127°	244°, 247°, 250°, 258°(d.)	258°, 262°
α-phenyl-o-toluindole	126°	232°(d.)	255° -256°
α-phenyl-p-toluindole	135°	262°(d.)	——

The picrates are unstable, decomposing readily into their constituents and being consequently difficult to obtain pure. In addition, they do not serve to distinguish between α-phenyl indole and α-phenyl-o-toluindole. The latter objection also applies to the benzylidene compounds.

The "nitroso-compounds" are of very uncertain melting-point, since they melt with decomposition at a high temperature, and have not been obtained pure until now (see page 99).

In the present work it was therefore necessary to prepare a few derivatives of these indoles, in order to furnish a satisfactory series of compounds, by means of which a given indole of the group under examination could be identified with certainty.

The compounds chosen for preparation and examination were the "nitroso-compounds" and their acetyl and benzoyl derivatives, and the azo-derivatives.

(a) Preparation of 2-phenyl-6-methyl indole picrate.

This substance had not been made before but

was/

was prepared according to the directions of Bischler (Ber., 1892, 25, 2860).

2-Phenyl-6-methyl indole (0·25 gm.) and picric acid (0·3 gm.) were dissolved separately in absolute alcohol and the two solutions mixed. A blood-red solution was immediately produced. This was evaporated to dryness at room temperature, and the residue, consisting of picrate and unchanged reactants, was recrystallised from a mixture of benzene and petrol ether, when the former compound was obtained as deep purple needles melting sharply at 145·5°. The substance was found to be extremely soluble in alcohol, and to be easily decomposed by water, or even on standing for several days in the dry state in a stoppered sample-tube.

The yield obtained was poor (0·083 gm.) and only amounted to 15% of the theoretical. This was due to heavy loss on recrystallisation and to the incompleteness of the reaction. The latter appeared to be easily reversible, as witness the spontaneous decomposition of the picrate on standing, with separation of indole and picric acid. On this account the pure substance could only be obtained by picking out the crystals by hand, a circumstance which made undesirable the use of these picrates as characterising derivatives.

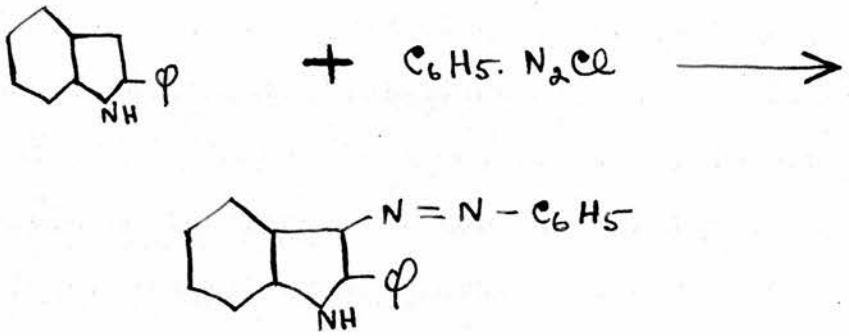
Nitrogen analysis:- (Micro-Dumas).

Found	12·9%
Calculated	12·84%

(b)/

(b) Preparation of Azo-compounds.

Plancher and Soncini, Gazz., 1902, 32(2), 447.



(1) Preparation of 2-phenyl-3-benzeneazo-indole.

Aniline (1 gm.) was dissolved in concentrated hydrochloric acid (5 c.c.) and water (2 c.c.) added. The solution was cooled under the tap and then excess of solid sodium nitrite added. The mixture was allowed to stand at 10° for 5-30 minutes to allow the diazotisation to be completed. Excess nitrous acid was now destroyed by addition of urea until evolution of gas ceased or until the mixture no longer turned potassium iodide - starch paper blue. A solution of 4 gms. of sodium acetate in a little cold water was now added. (If a yellow precipitate appeared at this stage (diazoaminobenzene $C_6H_5.N:N.NH.C_6H_5$), incomplete diazotisation of the aniline was thereby indicated and the whole preparation had to be repeated from the beginning).

To the resultant clear, pale yellow solution was added a suspension of 1 gm. of 2-phenyl indole in alcohol, and the mixture shaken up. After standing for a few minutes it was poured into water and/

and the precipitate filtered off, dried, and recrystallised repeatedly from ligroïn. It separated in dark red cubes which formed a yellow powder on being ground up.

The yield obtained was 1·25 gms. or 82% of the theoretical. The observed melting-point, after the first recrystallisation from ligroïn, was 137°-138° and this did not change after a second recrystallisation, this time from benzene. A third recrystallisation (from ligroïn) however, gave a product melting at 164°-165°, agreeing fairly well with Plancher and Soncini's quotation, 166°.

This sudden change in melting point from 137°-138° to 164°-165° after remaining constant through two recrystallisations from different solvents was remarkable, and was observed only once. At all other attempts to prepare this azo-compound, the product melting at 137°-138° was obtained, and this melting-point did not rise on further recrystallisation.

Probably the two products are geometrical isomers

the latter being the cis-form (m.p. 137°-138°) and the former the trans- form (m.p. 164°-165°).

The azo-compounds were found to be insoluble in water, ligroïn (cold) or petrol ether (hot or cold), but very soluble in alcohol, ether, chloroform, carbon/

carbon disulphide, benzene, pyridine, glacial acetic acid, dilute acetic acid and amyl acetate. They were recrystallised from ligroïn, in which solvent they are moderately soluble at the boiling-point.

The substances gave pale yellow solutions in glacial acetic acid, which became red on addition of water. A red colouration was also obtained on boiling any of the azo-compounds with concentrated hydrochloric acid, with the result that the substances gave a red "pine-splint reaction" independent of the true indole test.

(2) Preparation of 2-phenyl-3-benzeneazo-5-methyl indole.

This was prepared in exactly the same way as 2-phenyl-3-benzeneazo indole, from 2-phenyl-5-methyl indole and diazotised aniline. The substance, before recrystallisation, melted at 180°-182·5°, and after one recrystallisation at 193° (sharp). This increase of 10°-13°in the melting-point, in one recrystallisation, may possibly be due to an isomerisation of the cis- form to the trans- form, but there is no real evidence for this in the observations quoted.

Further recrystallisation did not raise the melting-point, and the substance was obtained in long, narrow, golden brown prisms resembling long needles. On crushing the crystals a bright golden yellow/

yellow powder was obtained.

The yield from 1 gram of the indole was 1·47 gms. representing 98% of the theoretical.

Nitrogen analysis:- (Ter Meulen)

Found	N 13·3%
Calculated	N 13·5%

(3) Preparation of 2-phenyl-3-benzeneazo-6-methyl indole.

This was prepared by the condensation of benzenediazonium chloride and 2-phenyl-6-methyl indole, according to the method described above for the 5-methyl derivative.

The product obtained melted before recrystallisation at about 135°, and after one recrystallisation from ligroïn at 138·5°-142·5°. A second recrystallisation, however, raised the melting-point to 169·5°-171°, and a third recrystallisation gave a product melting at 177° (sharp). A fourth recrystallisation did not raise the melting-point further.

These observations seem to suggest that the azo-compound exists in two forms, one melting about 138° and being converted into the other (m.p. 177°) by the action of heat during the recrystallisations from ligroïn (b.p. 100°-120°).

The final product was obtained as dark brown cubes, which gave a golden brown powder on crushing.

The/

The yield obtained was 1·21 gms. of azo-compound from 1 gm. of indole, this representing 81% of the theoretical.

Nitrogen Analysis:- (Micro-Dumas method)

Found	N	13·4%
Calculated	N	13·5%

(4) Preparation of 2-phenyl-3-benzeneazo-7-methyl indole.

Benzenediazonium chloride was condensed with 2-phenyl-7-methyl indole to give this azo-compound, the procedure employed being exactly the same as for the isomeric compounds described above.

The melting-point of the crude product was not taken, but after recrystallisation from alcohol the substance melted at 153°. Further recrystall-:isation from ligroïn gave a product melting at 155° (sharp).

In this case therefore there was no indication of the formation of two modifications of the compound.

The substance crystallised from ligroïn and alcohol as long dark-red irregular plates occurring in clusters resembling those of the osazones. On crushing the crystals a salmon-red powder was obtained.

The yield from 1 gm. of indole was 0·76 gm., representing 51% of the theoretical.

Nitrogen Analysis:- (Micro-Dumas method)

Found	N	13·4%
Calculated	N	13·5%

(c) Preparation of the Isonitroso-compounds.

Numerous references, e.g. Bischler, Ber., 1892, 25, 2860; Möhlau, Ber., 1882, 15, 2480; Möhlau, Ber., 1885, 18, 166; Fischer and Schmitt, Ber., 1888, 21, 1073.

The isonitroso-compounds were easily prepared by dissolving the indole in glacial acetic acid and adding excess of powdered sodium nitrite. On addition of water, the isonitroso-compound was precipitated as a bright yellow substance, which was filtered off, washed with water, alcohol and ether, and then recrystallised.

On account of the characteristic insolubility of the isonitroso-compounds in all the usualsolvents, previous workers have never prepared these substances in a pure state. Möhlau recrystallised them from a mixture of aniline and glacial acetic acid, while Fischer used the latter solvent alone. It was found, however, in this research, that if the com-:pounds were recrystallised from amyl acetate they could easily be obtained in a state of absolute purity, and with much higher melting-points than those previously quoted (22° higher in one case). There was no dubiety whatever about the identity of these purified products with those obtained by previous workers, since the observed melting-points before recrystallisation from amyl acetate agreed approx-:imately with those quoted in the literature.

This/

This new purification process represents an important advance in the identification of the indoles concerned, since the melting-points of the purified isonitroso-compounds, although really decomposition temperatures, are now easily reproducible, in contrast with the widely varying values previously found. The purified isonitroso-compounds can thus be used to identify these indoles with certainty. The significance of this point becomes clear when it is remembered that the phenyl indoles are either so soluble or insoluble in all the ordinary solvents, and are so difficult to distil, that it is often practically impossible by crystallisation or distillation to isolate the indole itself from reaction mixtures, especially where considerable charring has occurred.

The indole present, however, can be easily isolated in almost theoretical yield in the form of the isonitroso-compound, on account of the insolubility of the latter in all the usual solvents (see pages 23, 89).

To place the identification of the indole beyond dispute, the isonitroso-compound can be acetylated and benzoylated, with production of well-defined, easily purified derivatives with sharp melting-points (see pages 107, 110).

This method of identifying an indole was used in this research to establish the fact that the α-phenyl-m-toluindole made by Bischler's method was identical/

identical with that obtained by the Fischer synthesis, the product from the latter reaction being subsequent-:ly shown to be the 6-methyl derivative. The substance obtained by the former method could not be isolated in a pure state for a melting-point or mixed melting-point determination. The crude indole was therefore converted into the isonitroso-compound, which was shown to have the same melting-point as the corresponding compound of the α-phenyl-m-toluindole made by Fischer's method. A mixed melting-point of the two products showed no depression, but to prove their identity conclusively each was acetylated and the two derivatives shown by melting-point and mixed melting-point to be the same substance. In this way it was shown that the α-phenyl-m-toluindole made by Bischler's method was the 6-methyl compound and not the 4-methyl derivative, a fact which would have been difficult to establish by any method involving the isolation of the pure indole itself.

The complete purification of the isonitroso-compounds, if these had been prepared from residues or the rejected mother-liquors obtained in the purification of the indoles, frequently required four or five recrystallisations, but it was found that this could be avoided by the following treat-:ment:

Very impure 2-phenyl-3-isonitroso indole (m.p. about 240°) was dissolved in a small quantity of/

of pyridine at the boiling-point. To the very dark resultant solution was now added just sufficient water to cause cloudiness. Another drop of pyridine was added, the solution boiled, and then allowed to cool. Precipitation of dark solid material occurred and the mixture was filtered. The black sludge left on the filter-paper was immediately washed with ether and drained at the pump, leaving a clean yellow compound, which melted at 277° (with decomposition), and was obtained pure (m.p. 280°) by one recrystallisation from amyl acetate.

The isonitroso-compounds were usually obtained in the first instance as amorphous-looking yellow powders, but on recrystallisation from amyl acetate they separated in the form of minute golden yellow or orange coloured, diamond-shaped crystals occurring in star-shaped clusters. These compounds are always described in the literature as yellow substances, but this is only true of the impure products previously obtained. The pure compounds are definitely orange in colour, this becoming deeper on recrystallisation from boiling amyl acetate. (See page 99).

The most characteristic features of these substances are their yellow or orange colour, their high melting-points (230°-280° with decomposition) and their insolubility in all the common solvents. They are insoluble in water, alcohol, ether, chloroform/

chloroform, carbon disulphide, petrol ether, benzene, etc., sparingly soluble in cold glacial acetic acid, acetone, and cold amyl acetate; fairly soluble in hot glacial acetic acid, hot amyl acetate and cold aniline; and very soluble in hot aniline, pyridine (hot or cold) and molten camphor. Solutions in the last three solvents are dark red, the pyridine solutions being especially dark. This, however, is merely a concentration effect. A saturated pyridine solution is almost black, the colour changing on dilution through dark red, red, orange, light orange and yellow to very pale yellow.

Recrystallisation may be effected by the use of

(1) a very large quantity of alcohol
(2) glacial acetic acid (Fischer)
(3) aniline
(4) a mixture of aniline and glacial acetic acid (Möhlau)
(5) amyl acetate.

Only the last method yields the pure substances, however.

Table of melting-points of the isonitroso-compounds.

Column I gives the melting-points previously quoted. Column II gives those obtained in this research by recrystallisation from amyl acetate until of constant melting-point.

Isonitroso/

Isonitroso-compound of:-	Column I.	Column II.
2-phenyl indole	244°, 247° 250°, 258°	280°
2-phenyl-4-methyl indole	previously unknown	
2-phenyl-5-methyl indole	262°	273°
2-phenyl-6-methyl indole	previously unknown	237°
2-phenyl-7-methyl indole	232°	244°

Very characteristic of these isonitroso-compounds is the manner in which they decompose immediately after melting, with production of a dark brown liquid which froths up the melting-point tube. Although really decomposition temperatures, these readings are quite reproducible if the bath is preheated to 10°-20° below the melting-point before inserting the melting-point tube.

In order to prove conclusively by independent evidence that the substance obtained melting at 280° was really the same as Fischer's "nitroso-α-phenyl indole (m.p. 258°)", the compound was sent to Germany for analysis. The analysis figures returned gave, on calculation,

C 75·5% H 4·7% N 12·3%

while those required for 2-phenyl-3-isonitroso indole ($C_{14}H_{10}ON_2$) are

C 75·7% H 4·5% N 12·6%

The two new isonitroso-compounds prepared in this/

this research were analysed by the author, with the following results. Nitrogen alone was determined, as this was considered sufficient, there being no dubiety about the constitution of the compounds concerned. The Ter Meulen method was tried first but found to give consistently low results, an observationparalleled by that of W. Pursell (Thesis, Edinburgh, 1933) that high-melting nitro-compounds of the naphthalene series could not be analysed by this method.

The absolute micro-Dumas method of Fritz Pregl was thereafter employed exclusively for all nitrogen determinations.

Nitrogen analysis of 2-phenyl-3-isonitroso-4-methyl indole:-

Found	N	11·8%
Calculated	N	11·9%

Nitrogen analysis of 2-phenyl-3-isonitroso-6-methyl indole:-

Found	N	11·9%
Calculated	N	11·9%

To find out how the yield of isonitroso-compound compared with the amount of indole started with, 2-phenyl-5-methyl indole (4·00 gm.) was dissolved in cold glacial acetic acid and treated with a cold concentrated solution of sodium nitrite. The deep red solution obtained was poured into 500 c.c. of/

of water and the resultant yellow precipitate filtered off. After washing with water and alcohol this was dried and found to melt at 272°-273° (decomp.). The yield obtained was 4·00 gms., representing 88% of the theoretical. The substance thus obtained was practically pure since the highest melting-point obtainable, after recrystallisation from amyl acetate, is 273° (d.). Bischler, nevertheless, quotes this melting-point as 262° (loc. cit.).

The isonitroso-compounds are amphoteric in nature, being feebly basic on account of the tertiary nitrogen atom of the indole nucleus and feebly acidic on account of the -NOH group. They dissolve in cold concentrated sulphuric acid with production of a red solution. Sodium hydroxide (8%) dissolves the compounds slowly on boiling, dark red solutions of the sodium salts being obtained.

With Ehrlich's reagent the isonitroso compounds give a yellow colouration, which becomes red on warming, but they do not give the pine-splint reaction, in conformity with most other 2:3-disubstituted indoles.

The oxidation of these substances has already been described (page 56 et seq.), and other properties are discussed in Part III in connection with the evidence regarding their structure.

The isonitroso-compounds can also be acetylated and benzoylated as follows:-

(Spica/

(Spica and Angelico, Gazz., 1899, 29,(2), 59.)

Benzoylation of Isonitroso-compounds.

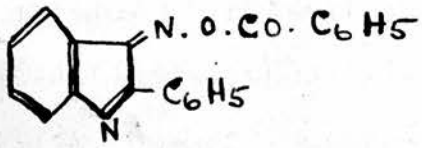
The isonitroso-compound (0·5 gm.,) was dissolved by boiling in 25 c.c. of 2N. sodium hydroxide, and the resultant dark red solution cooled. About 1 c.c. of benzoyl chloride was added and the mixture shaken until it became nearly colourless and a red solid separated out. (Care must be taken not to use a large excess of benzoyl chloride as it is difficult to remove it completely from the benzoyl derivative if the latter is heavily contaminated with it.)

The solution was now filtered, and the residue washed well with dilute sodium hydroxide solution and then with water. It was then dried and recrystallised from benzene or petroleum ether, or a mixture of the two. Benzene was found to be the best recrystallising medium except for very small quantities of material, and completely removed any adhering benzoyl chloride. It was very inconvenient, however, for recrystallising very small quantities of substance, on account of the practical difficulties associated with the recrystallisation of a compound from 1-2 c.c. of a volatile solvent in which it is quite markedly soluble, even in the cold. In such cases it was much easier to use ligroïn, although, unfortunately, this solvent was found to be incapable of removing completely/

completely large amounts of adherent benzoyl chloride.

The benzoyl derivatives formed dark-red needles with sharp melting-points, and were easily obtained in excellent yield.

2-Phenyl-3-benzoyloximo-indolone.

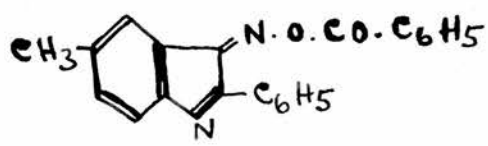


This was prepared as described above from 0·56 gm. of 2-phenyl-3-isonitroso indole. A yield of 0·59 gm. was obtained, representing 72% of the theoretical. The substance melted at 153°, as compared with Spica and Angelico's quotation, 151°-152°. A nitrogen determination was carried out, since the compound had only been made once before and the analysis figures quoted by Spica and Angelico (found, N,9·18%; calculated, N,8·60%) were unconvincing.

The figures obtained in this research by the micro-Dumas method were:-

Found	N 8·52%
Calculated	N 8·60%

2-Phenyl-3-benzoyloximo-5-methyl indolone.



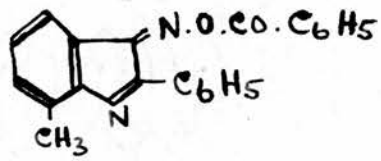
This/

This compound was prepared according to the method described above, and was obtained as red needles melting at 159°-160°. The yield obtained from 0·5 gm. of 2-phenyl-3-isonitroso-5-methyl indole was 0·61 gm., this representing 85% of the theoretical.

Nitrogen analysis:- (Micro-Dumas method)

Found	N 8·42%
Calculated	N 8·24%

2-Phenyl-3-benzoyloximo-7-methyl-indolone.

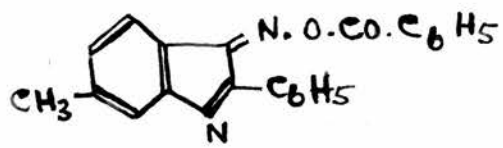


This isomer was also obtained as red needles, melting at 163°. The yield from 0·5 gm. of 2-phenyl-3-isonitroso-7-methyl indole was 0·61 gm., representing 85% of the theoretical.

Nitrogen analysis:- (Micro-Dumas method)

Found	N 8·35%
Calculated	N 8·24%

2-Phenyl-3-benzoyloximo-6-methyl-indolone.



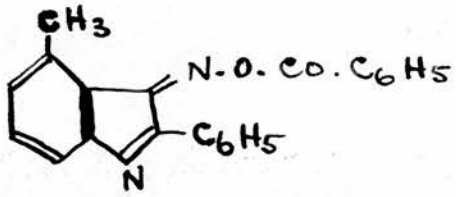
This compound was obtained as red needles indistinguishable visually from its isomers. It melted at 142°-143°, and was obtained in a yield of 96%/

96%, 0·5 gm. of 2-phenyl-3-isonitroso-6-methyl indole giving 0·69 gm. of the substance.

Nitrogen analysis:- (Micro-Dumas method)

Found	N 8·25%
Calculated	N 8·24%

2-Phenyl-3-benzoyloximo-4-methyl indolone.



Like its isomers this compound was obtained as gleaming red needles and melted at 145·5° after two recrystallisations from a mixture of benzene and ligroïn.

Nitrogen Analysis:- (Micro-Dumas method)

Found	N 8·12%
Calculated	N 8·24%

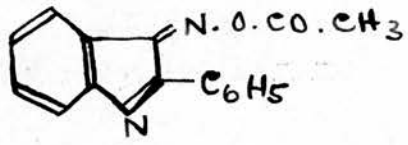
(2) Acetylation of Isonitroso-compounds.

The isonitroso-compound was boiled under reflux with acetic anhydride until a homogeneous red solution was obtained. This was poured into water, when a red oil separated. Solid sodium carbonate was now added until all the acetic anhydride had been converted into sodium acetate and the solution was alkaline. The red oil thereupon solidified to form hard crystals, which were filtered off, washed well with water, dried, and recrystallised from ligroïn.

The/

The acetyl derivatives formed dark red needles, insoluble in cold ligroïn, and only sparingly soluble in hot ligroïn.

2-Phenyl-3-acetyloximo-indolone.



This was prepared as described above, when it was obtained as red needles melting at 117°. The yield obtained from 0·5 gm. of 2-phenyl-3-isonitroso indole was 0·39 gm., this representing 65% of the theoretical.

The melting-point quoted by Spica and Angelico is 121°, but the melting-point, 117°, observed in this research could not be raised by further recrystallisation.

The analysis figures quoted for this compound by the above-mentioned authors are also inadequate, viz.,

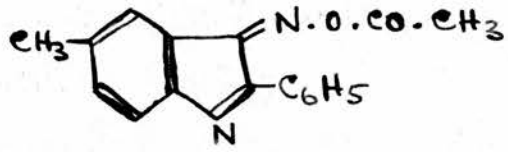
N 10·60% (calculated); N 11·04% (observed).

The nitrogen content of the compound was therefore determined anew by the micro-Dumas method, with the following result.

Found	N 10·5%
Calculated	N 10·6%

2-/

2-Phenyl-3-acetyloximo-5-methyl-indolone.

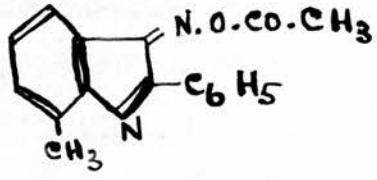


Prepared as above, this compound was also obtained as red needles, and melted sharply at 169·5°. The yield obtained from 0·5 gm. of 2-phenyl-3-isonitroso-5-methyl indole was 0·375 gm., representing 64% of the theoretical.

Nitrogen analysis:- (Micro-Dumas method)

Found	N 9·9%
Calculated	N 10·1%

2-Phenyl-3-acetyloximo-7-methyl-indolone.

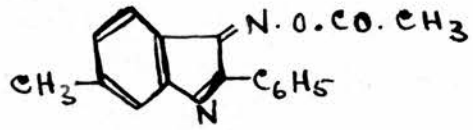


This compound was prepared as described above, and obtained as red needles melting at 122.5°. The yield obtained from 0·32 gm. of 2-phenyl-3-isonitroso-7-methyl indole was 0·35 gm., this being 93% of the theoretical.

Nitrogen analysis:- (Micro-Dumas method).

Found	N 10·3%
Calculated	N 10·1%

2-Phenyl-3-acetyloximo-6-methyl-indolone.

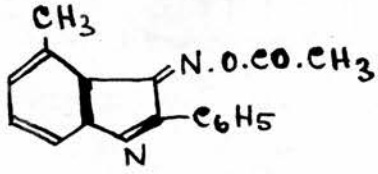


Prepared in the same way as its isomers described above, this substance was obtained as red needles melting at 118°-119°. The yield obtained from 2-phenyl-3-isonitroso-6-methyl indole was 0·575 gm., this being 95% of the theoretical.

Nitrogen analysis:- (Micro-Dumas method)

Found	N	10·3%
Calculated	N	10·1%

2-Phenyl-3-acetyloximo-4-methyl-indolone.



This substance was also obtained as gleaming red needles, and melted at 142°, the yield from 0·5 gm. of 2-phenyl-3-isonitroso-4-methyl indole being 0·55 gm., or 93% of the theoretical.

Nitrogen analysis:- (Micro-Dumas method)

Found	N	10·0%
Calculated	N	10·1%

DISCUSSION.

Regarding the relative efficiency of the four methods of preparing indoles discussed in the previous section, little needs to be added to what has already been said. It is recognised that no general criticisms can be based on the experimental material of this thesis alone, since a synthesis which serves admirably for one type of indole derivative may be comparatively useless for the preparation of another - and all the indoles prepared in this research belong to the same type.

Bischler's method does not appear to have attracted great favour in the past, which is not surprising in view of its somewhat limited applicability. In addition, it involves the use of the lachrymatory reagent, ω-bromacetophenone. The greatest difficulty associated with the synthesis, however, is the fact that the crude product cannot be purified by recrystallisation and must be distilled, and at the temperature at which the distillation is conducted, the impurities present in the crude indole decompose to form a thick black tar which bumps very badly. In an Anschütz flask, which Bischler recommends, this is not easy to prevent, while the high melting-points of the indoles and their small volatility combine to make impossible the use of a Claisen flask, in which this can be somewhat controlled.

(Note:- A very simple but effective method

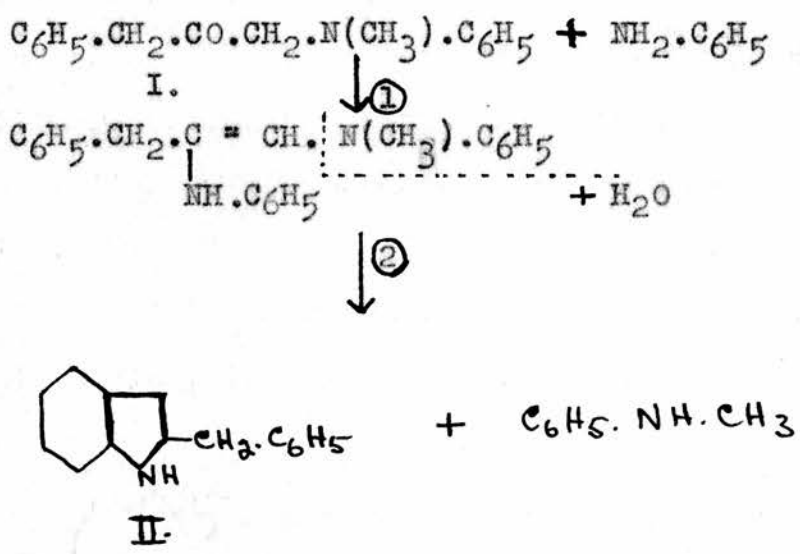
of/

of controlling bumping during a vacuum-distillation was found to be the insertion, through the main neck of the Claisen flask, of an ordinary glass spiral such as is used in the fractionating column of a Wittmar distilling flask. The spiral reached from the bottom of the Claisen flask to above the side limb, while there was just sufficient room down the axis for the insertion of a capillary leak. Using this device, the distillation could be carried out much more rapidly, no impure material being carried over into the distillate, despite severe and continuous bumping. Unfortunately, the method was useless for distilling very thick liquids, as one heavy bump choked the neck of the flask almost completely. The spiral acts as a continuous series of baffle plates, and in this respect is much simpler than the modified Claisen flask provided with fixed internal glass projections recently described in a Japanese journal.)

In a recent paper by Julian and Pikl (J.A.C.S., 1933, 2105) on the preparation of α-benzyl-indoles by Bischler's method, some anomalous results are described, as a result of which these authors challenge Bischler's mechanism of the reaction, and are now engaged in an investigation of the subject.

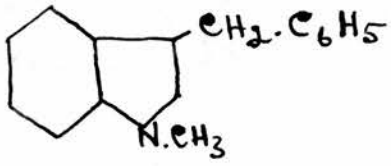
According to Bischler, it is the amine with which the anilide is boiled that forms the benzene ring portion of the indole, and on treating the anilide/

anilide I. with aniline the reaction proceeds as shown:-



II.

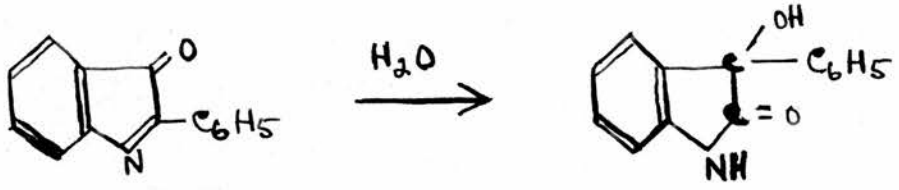
In addition to the product II, however, Julian and Pikl obtained a 30% yield of the indole III. when the reaction was carried out at 128°, this yield being less when a higher temperature was employed.



III.

Nevertheless, this result is not necessarily in conflict with Bischler's mechanism, for the following reasons. Firstly, the production of an N- methyl indole is easily explained by the action on substance I. of the methyl-aniline liberated in the formation of the indole II; the diminished yield of indole III. on raising the temperature being readily understood should reaction ① have a higher temperature coefficient than reaction ②.
Secondly, a possible migration of the benzyl group from/

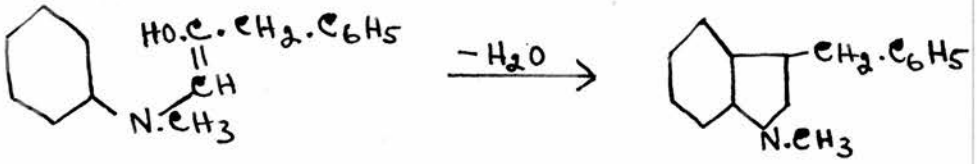
from the α- to the β- position would not be without parallel, since β-phenyl indole gives α-phenyl indole on fusion with zinc chloride, while β-phenyl ~~indoxyl~~ dioxindole is formed from α-phenyl indolone merely on boiling an alcoholic solution of the latter containing a little caustic soda. (Kalb and Baeyer, Ber., 1912, 45, 2150.)



At the same time it cannot be denied that these authors have also obtained an almost theoretical yield of N-methyl-α-benzyl-indole by the action of methyl-aniline on the above-mentioned ketone I. at 190°-200°, no migration of the benzyl group to the β-position being observed.

It is much more probable, however, that Bischler's mechanism is correct, and that the production of N-methyl-β-benzyl-indole was due to an altogether different reaction such as the simple dehydration shown below.

$$C_6H_5.CH_2.CO.CH_2.N(CH_3).C_6H_5 \rightleftharpoons$$



It will be noted that the yield of the latter indole was greatly reduced when a higher temperature was used. This result is at once explained if we assume/

assume that, of the two competing reactions, the anilide condensation has a higher temperature coefficient than the dehydration process.

Since Bischler's preparations were all made at the boiling-point, i.e. above 180°, and as only one indole was formed in each of his experiments despite the use of different amines for forming the anilide and for boiling with it, it is apparent that the anilide condensation (1) must be very rapid, otherwise the indoles corresponding to the amines liberated by this reaction would also have been obtained. It is apparent, therefore, that the suggestions made above for explaining Julian and Pikl's results are not entirely without justification.

Madelung's indole synthesis has the great advantage of simplicity, and reaches the desired product in one simple stage from very easily accessible common chemicals (if we exclude pure xylidines). If Madelung's yields of 60% are attained, the process is a considerable improvement on the older method of Fischer with its many stages, including diazotisation, reduction, hydrazone formation and zinc chloride fusion. In this research, however, the yields of the four indoles investigated, even when isolated as the isonitroso-compounds, never exceeded 7%, despite numerous attempts under different conditions. Failure in technique can scarcely be the reason for such a serious discrepancy/

discrepancy in a perfectly simple preparation described in detail by the author. More probably some essential point has been omitted from the latter's description, or else the synthesis is governed very largely by some unsuspected factor, perhaps a catalyst.

In the circumstances, therefore, while there is so much doubt on the subject, the matter must be left pending further evidence.

Trennkler's process, being merely a modification of Fischer's, is best discussed in that connection. All that need be said here is that the method is ineffective for synthesising the indole derivatives examined in this research, a finding which was fully anticipated on general grounds before the method was attempted.

In the opinion of the author, and in the absence of confirmatory evidence that 60% yields of indoles can be obtained by Madelung's process, the best method of preparing indoles is still that of Fischer, despite the number of stages involved in the synthesis. Apart from the comparatively poor yields (25% - 40%) obtained in the preparation of the necessary hydrazines, the process was very satisfactory once the correct fusion temperature had been found for any particular case.

Interesting features of the Fischer synthesis are the observations generally made that the more complex the indole, the more heavily it is loaded with/

Madelung does not specify whether it is the reaction mixture or the heating bath that is to be therein 350 - 380°C. It is assumed that the latter is meant.

with substituents, and the more condensed rings it contains, the easier it is to form. Reference to this point is made elsewhere (page 8).

As regards characterising derivatives of the indoles prepared in this research, it is now felt that this has been put on a more satisfactory footing. As has been pointed out already (page 92), the picrates are unsatisfactory and the benzylidine compounds of little value for characterisation, while the employment of the "nitroso"- compounds has so far been somewhat restricted by the difficulty of obtaining consistent melting-points. This drawback has now been removed, and the utilisation of these derivatives for identification purposes is strongly recommended. In addition, by the use of these compounds it is a simple matter to isolate any of the indoles in excellent yield from any charred, tarry or otherwise highly contaminated material, from which the isolation of the indole itself would be almost impossible. The "nitroso-compounds", moreover, can be benzoylated and acetylated, with production,in excellent yield, of crystalline and easily purified compounds of sharp and characteristic melting-point.

The azo-compounds described above (page 94) also form excellent characterising derivatives, but as they can only be prepared from the pure indoles themselves, they are not so convenient to use. By reference to the appended table, however, a good choice/

choice of characterising derivative or derivatives may readily be made, so as to distinguish with absolute certainty between any given pair of indoles on the list.

Melting-Points of Characterising Derivatives.

	Indole	Isonitroso	Acetyloximo	Benzoyloximo	Benzeneazo	Picrate
2-Phenyl	189°	280°(d.)	(121°) 117°	153°	164°-165°	127°
2-Phenyl-4-methyl	—	251°(d.)	142°	145·5°	—	—
2-Phenyl-5-methyl	216°	273°(d.)	169·5°	159°-160°	193°	135°
2-Phenyl-6-methyl	193°	237°(d.)	118°-119°	142°-143°	177°	145·5°
2-Phenyl-7-methyl	(118°-119°) 117°	244°(d.)	122·5°	163°	155°	126°

PART II.

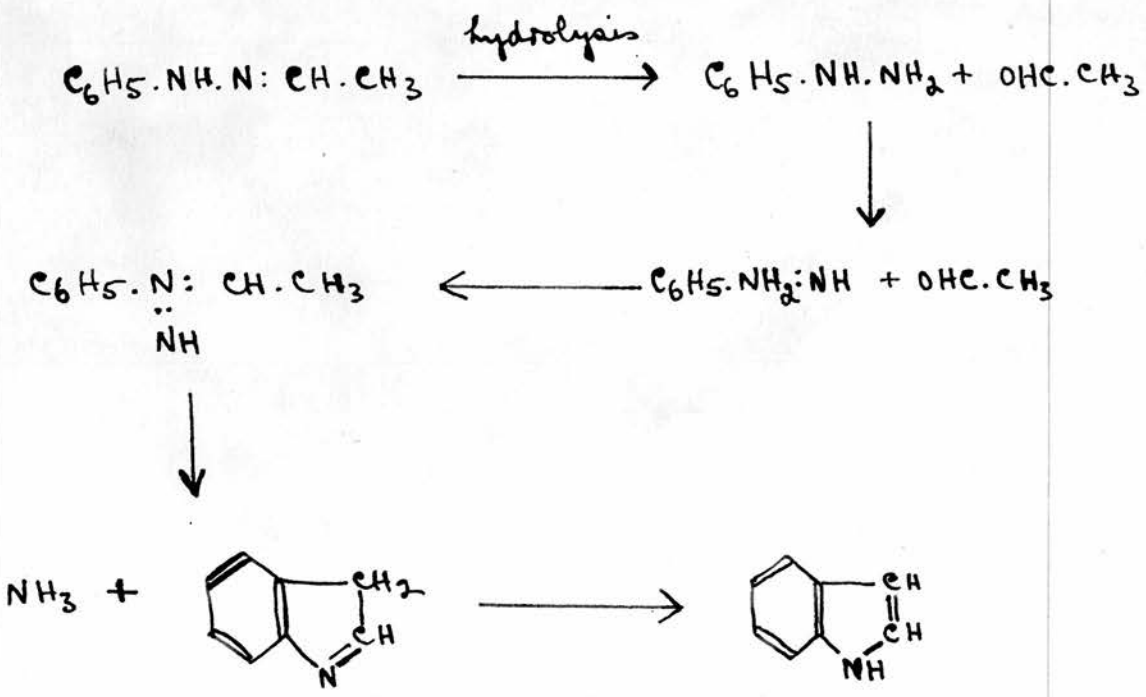
The Mechanism of the Fischer Indole Synthesis.

Introduction.

Four theories have been advanced to explain the course of this strange reaction - those of Brunner (1898), Reddelien (1912), Cohn (1919), and Bamberger and Landau (1919).

Robinson and Robinson (1918) have adopted the idea originally put forward by Brunner, adduced evidence in support of it, and may now justifiably claim the theory as their own. The four theories will be discussed in contra- chronological order.

Bamberger and Landau (Ber., 1919, 52, 1097) suggest the following mechanism:-



This preliminary hydrolysis, however, cannot take/

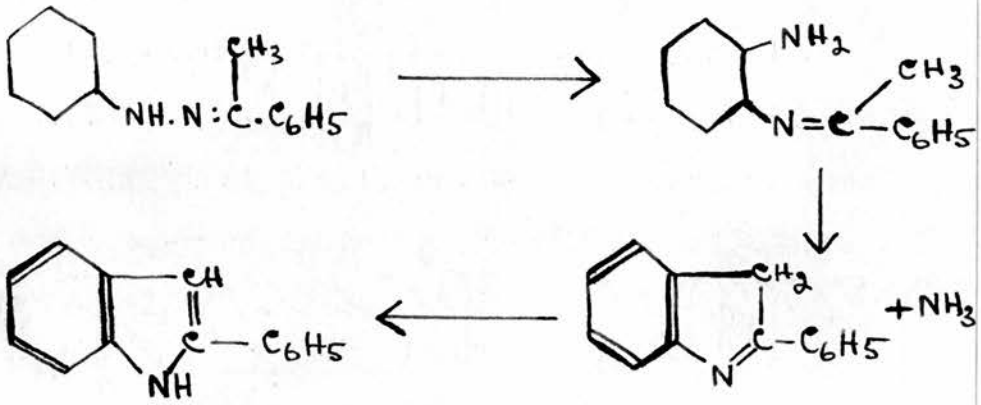
take place when the dry hydrazone is fused with anhydrous zinc chloride, and to evade that difficulty Bamberger proposed a direct re-arrangement of

$$C_6H_5.NH.N{:}\ CH.CH_3 \text{ to } C_6H_5.N{:}\ CH.CH_3$$
$$\quad\quad\quad

(2) The mechanism by which the ammonia is eliminated is not explained.

(3) The alternative suggestions of a preliminary hydrolysis or an intramolecular rearrangement are both highly improbable.

Cohn's theory ("Die Carbazolgruppe", 1919, page 12) assumes an ortho-semidine conversion, thus:-



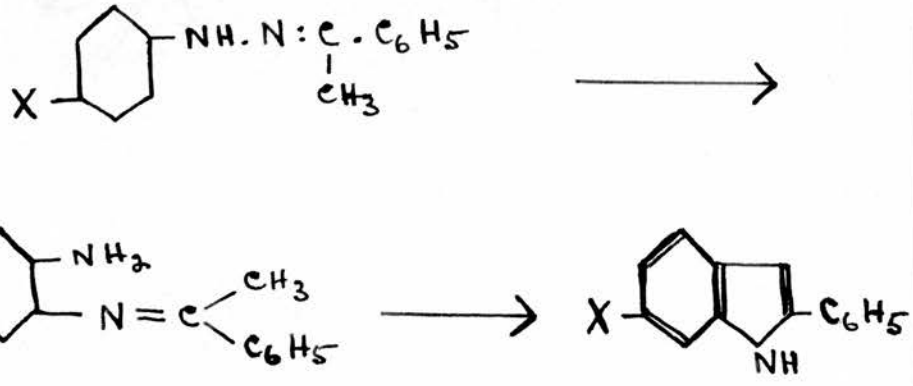
Hollins has objected that the failure to obtain any of the products of a para conversion, and the failure to obtain increased yields of indole in the case of para-substituted hydrazones tell against the theory. These criticisms have also been levelled at Robinson's mechanism and will be considered in that connection (see page 141).

An insuperable objection to the theory is its complete failure to account for the production of N-substituted indoles from hydrazones of the form $C_6H_5.NR'.N{:}CR''.CH_2R'''$.

In addition, Robinson points out that the theory "involves an alteration in the orientation of/

of substituents in the benzene ring, and this has been shown not to occur". This very important point is not further explained or amplified beyond the single sentence quoted, and so is apt to be overlooked. It will therefore be discussed here more fully.

According to present conceptions ortho-, meta-, and para- substituted hydrazones give rise respectively to 7-substituted, 4 (or 6)-substituted, and 5-substituted indoles. According to Cohn's theory, however, these hydrazones would be expected to give 4-substituted, 5 (or 7)-substituted and 6-substituted indoles respectively.



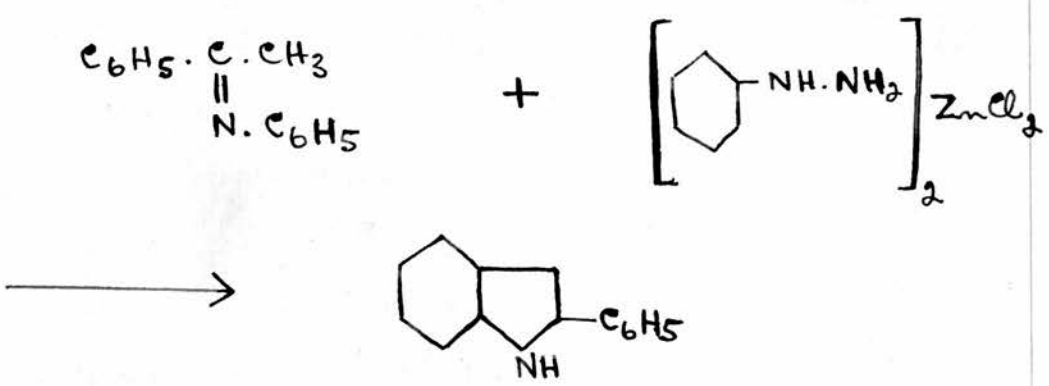
If Cohn's views were correct the accepted orientations of all known Bz-substituted indoles made by Fischer's method would have to be altered, since these are based, in most cases, solely on the assumption that an ortho-, meta-, or para- substituent X in the hydrazone will appear in the indole respectively ortho, meta, or para to the -NH- group.

That they are not correct is shown by independent/

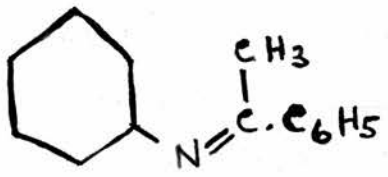
independent syntheses of the indoles in question. For example, α-phenyl-p-toluindole made by Bischler's method must be the 5-methyl compound, yet it is identical with the indole made from acetophenone-p-tolylhydrazone, which, according to Cohn's theory, should be the 6-methyl derivative.

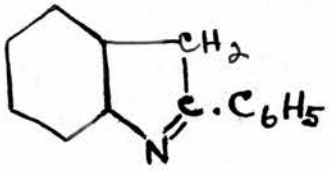
Actually, though Robinson does not say so, these two vital objections to Cohn's mechanism arise from the same source - the nitrogen atom lost from the hydrazone as ammonia is the one which ought to be retained in the indole ring.

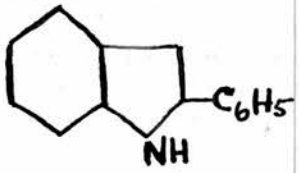
The theory of Reddelien (Ann., 1912, 388, 179) is based on the latter's observation that α-phenyl indole is produced by fusing together at 230° acetophenone-anil and phenylhydrazinezincichloride.



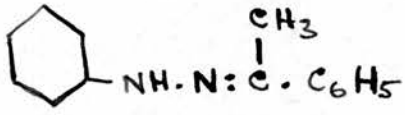
Reddelien explained the reaction as being due to the oxidising action of phenylhydrazine in removing two hydrogen atoms of the anil, yielding α-phenyl indole, aniline and ammonia.



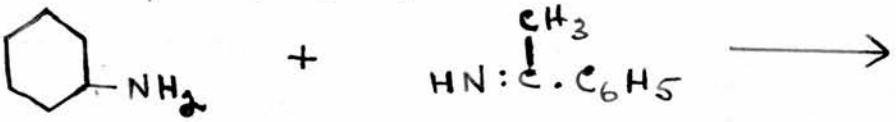


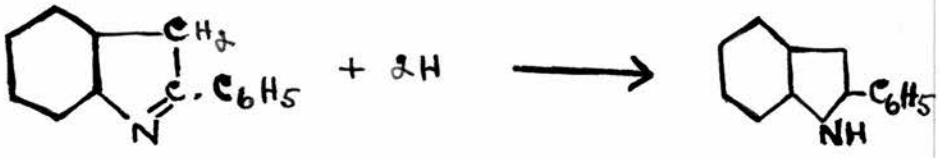


He therefore postulated this as one of the reactions involved in the Fischer synthesis of indoles from hydrazones, thus:-



Acetophenone-phenylhydrazone.

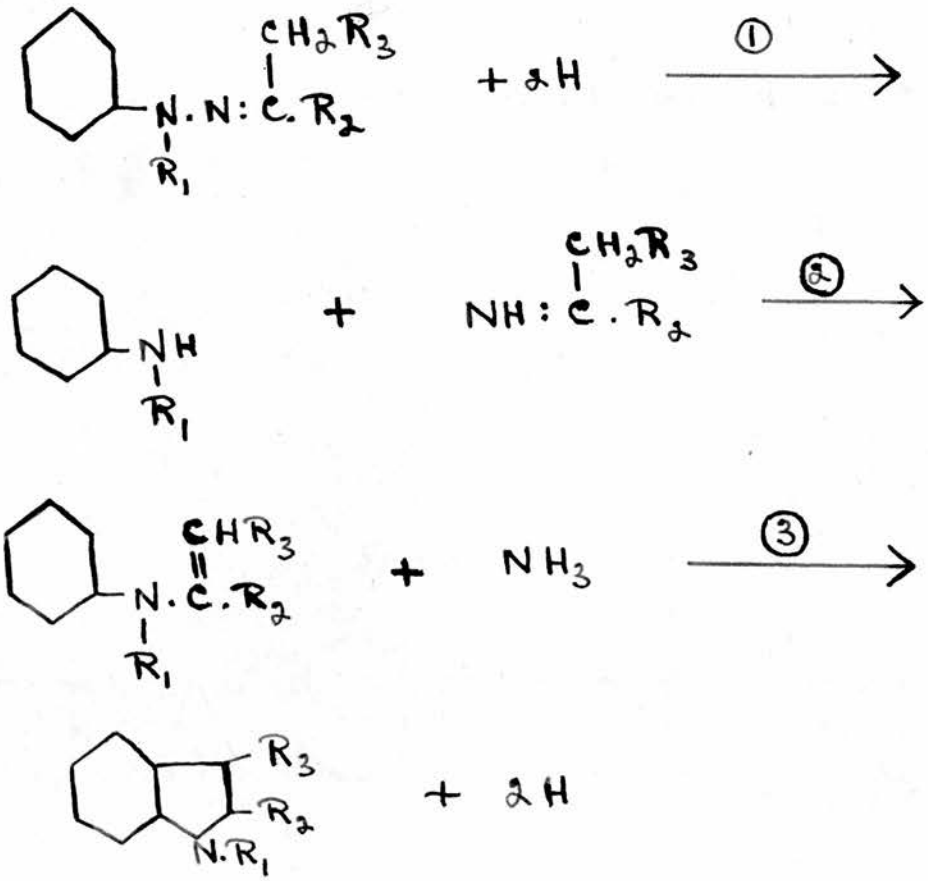




α-phenyl indole.

This mechanism, by a slight modification, accounts for the production of N-substituted indoles, as/

as in the general case:-

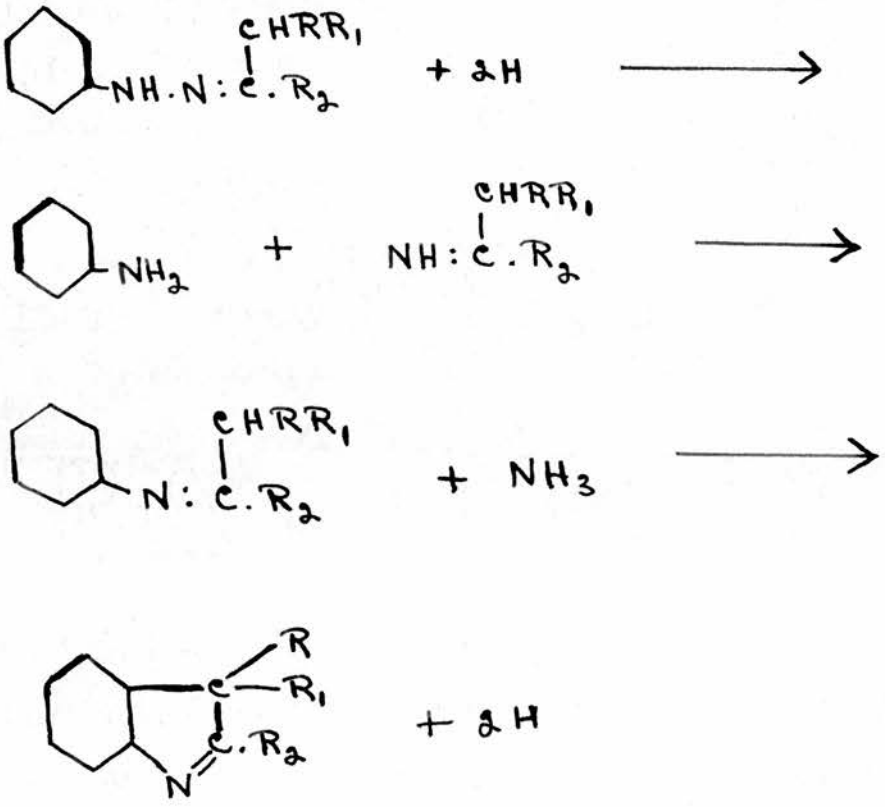


The hydrogen required for the initiation of the reaction is supposed to arise by the decomposition of a small part of the hydrazone, and as this hydrogen is used over and over again, only a minute amount of the hydrazone requires to be decomposed for the reaction to go forward to completion.

The browning which occurs in a Fischer fusion is looked upon as evidence for a preliminary decomposition of the hydrazone, which might lead to the production of the minimal amount of hydrogen required.

The chief protogonist of this theory is Hollins (loc. cit.), who brings forward the following arguments:-

1. When the hydrazones of α-alkylated ketones are subjected to a Fischer fusion, indolenines are formed instead of indoles, a reaction which is readily explained on Reddelien's theory in the following way:-



2. The theory accounts for the production of N-substituted indoles.

3. The mechanism given involves the loss, as ammonia, of the correct nitrogen atom of the hydrazone, namely, the tertiary one ($Ph.NH.N^{\mathbf{M}}.CR_1.CH_2R_2$).

4. The ease of formation of 3- disubstituted indolenines may be correlated with the generally observed/

observed great ease of oxidation of the group - C H R R_1. According to Reddelien's mechanism, it is precisely the oxidation of this group which is the central stage in the formation of the indolenines. (See above).

With regard to the first three points Reddelien's mechanism shows no advantage over that of Robinson, which also explains satisfactorily the production of indolenines (page 145) and N-substituted indoles, and involves the loss of the correct nitrogen atom. The fourth point is, at most, a very indirect one.

In addition, Hollins quotes three other reactions in support of Reddelien's theory, but as these can be explained equally well on the rival theory of Robinson, they throw no further light on the subject and will be omitted.

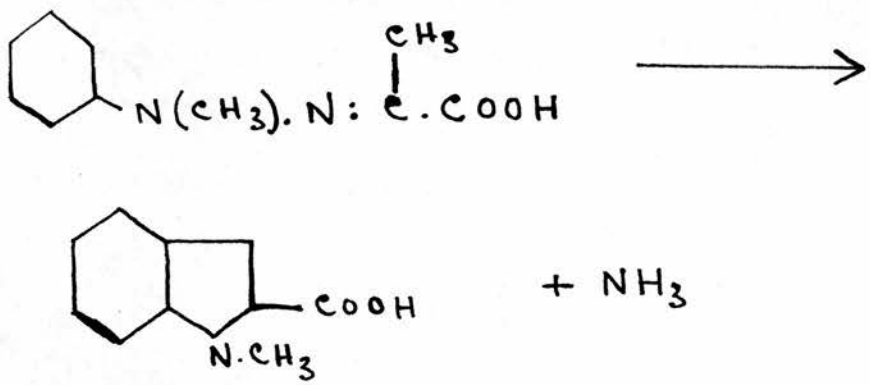
Robinson definitely criticises the Reddelien theory on the following grounds: To begin with, it does not seem very feasible. Secondly, it involves a fission of the hydrazone molecule, with subsequent reunion of the parts - in some cases an almost quantitative reunion. Thirdly, the ketone-imines and anilides are extremely sensitive to acid hydrolysis, yet in some cases in which the indole synthesis is carried out by means of hydrochloric or other acids, quantitative yields of indole are obtained, indicating the complete escape from hydrolysis/

hydrolysis of extremely sensitive intermediate compounds. This scarcely seems possible.

In addition, the theory involves a compensat-:ing oxidation and reduction, which do not follow each other immediately, but are separated by an intermediate condensation. Such reactions, accord-:ing to Robinson, are very difficult to effect in practice.

A very ingenious method of testing Reddelien's theory was devised by Bodforss, (Ber., 1925, 58 (1), 775).

A Fischer synthesis which takes place rapidly and easily in the solution phase was chosen, namely, the conversion of the methylphenylhydrazone of pyruvic acid into N-methyl indole-2-carboxylic acid by the action of aqueous hydrochloric acid.



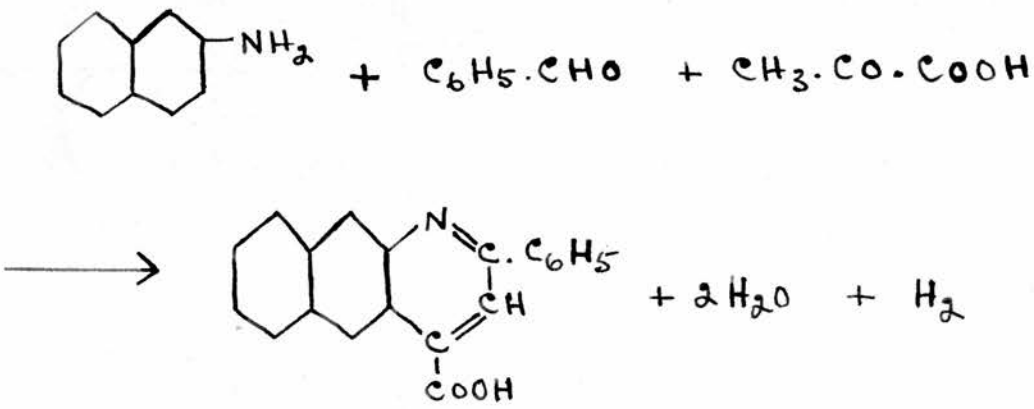
A piece of unplatinised platinum foil was immersed in 10% hydrochloric acid, coupled with a calomel electrode, and its potential measured. The platinum foil formed a kind of "air electrode" whose potential became fairly constant "after several hours/

hours or days".

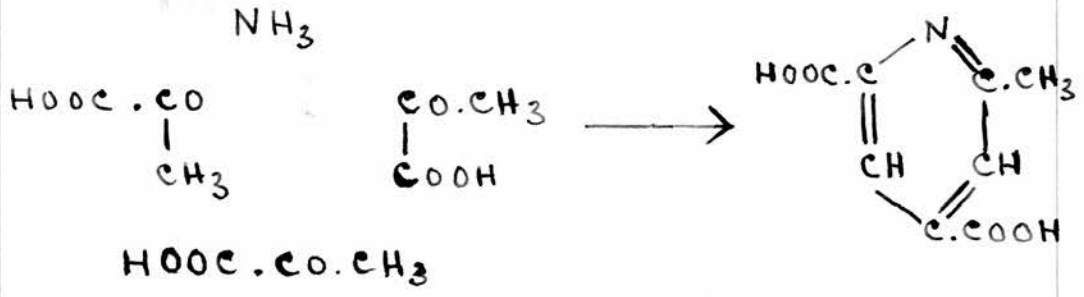
The hydrazone was now added, and the formation of the indole commenced almost at once. Now if an essential stage in this latter reaction were a reduction, some oxygen would be certain to be removed from the platinum foil, this lowering its potential. This was not observed.

To prove the validity of the method it was shown that in two analogous cases where hydrogen was formed, but used up and not set free, an electrode potential lowering did occur.

These cases were (a) the production of 2-phenylnaphthocinchonic acid by the interaction of benzaldehyde, pyruvic acid and β-naphthylamine in methyl alcohol solution,



and (b) the auto-condensation of ammonium pyruvate in aqueous solution:



$HOOC.CO.CH_3$

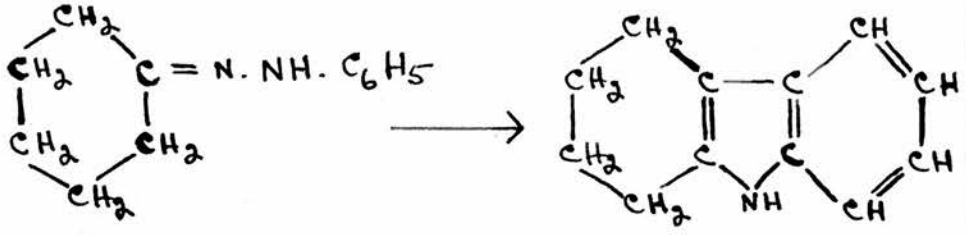
$+3H_2O + CO_2 + H_2$

In both cases cited above the hydrogen produced is not set free, but is used up in some further process - probably hydrogenation of the main product of the primary reaction.

The absolute values of the potentials measured, of course, have no significance, as we are not dealing here with a reversible ionic electrode process.

More direct and, perhaps, more trustworthy evidence against Reddelien's theory is the observation (Robinson, later also by Bodforss) that the addition, even in huge quantity, of another amine different from that supposed to be liberated from the hydrazone at stage (1) of the fusion, does not affect the result, and no indole corresponding to that amine is obtained.

For example, cyclohexanonephenylhydrazone yields pure tetrohydrocarbazole in presence of either p-toluidine, methylaniline or p-nitroaniline.



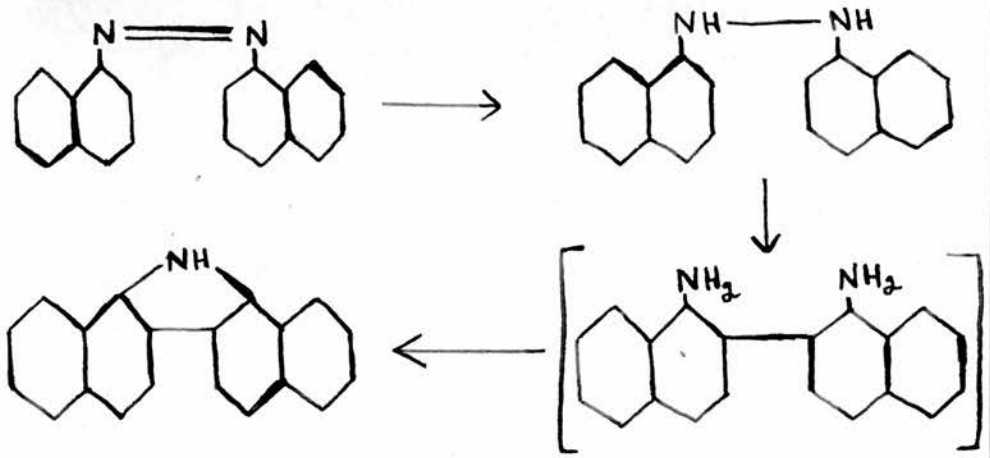
To explain this on Reddelien's theory it would have to be assumed that the aniline liberated from the hydrazone was much more reactive than any of the amines added. The erroneous nature of such an assumption is shown by the fact that the yield of nitrotetrahydrocarbazole/

nitrotetrahydrocarbazole from cyclohexanone-p-nitrophenylhydrazone is not affected by addition of aniline.

Thus in one case we must assume that aniline is more reactive than p-nitroaniline, and in the second case the reverse.

The yield of 2-methyl indole from acetonephenylhydrazone is also unaffected by the presence of p-toluidine.

Attention is also drawn by Robinson to the production of dinaphthacarbazole by the action of stannous chloride and concentrated hydrochloric acid on α-azo-naphthalene.

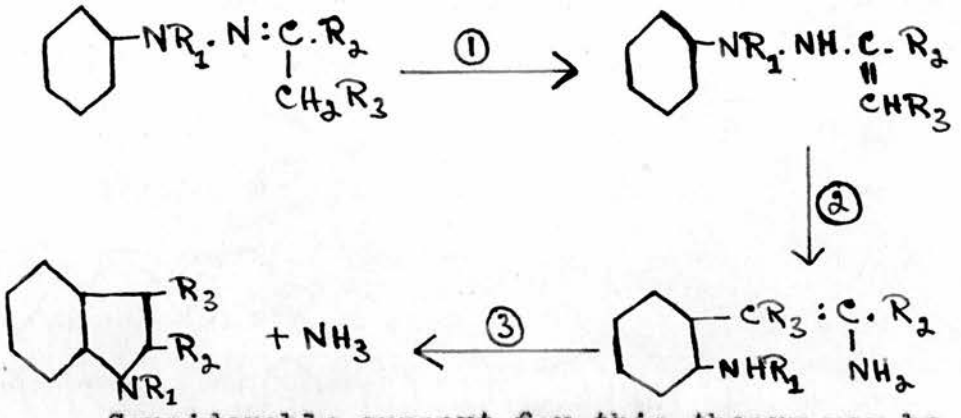


The mechanism given here is Robinson's. Reddelien's theory would involve an oxidation by removal of two hydrogen atoms as one stage of the reaction, and this, in presence of such a powerful reducing system as stannous chloride and hydrochloric acid seems scarcely feasible.

Robinson has also shown experimentally that the production of tetrahydrocarbazole from cyclohexanone-phenylhydrazone/

cyclohexanone-phenylhydrazone by the action of hot hydrochloric acid (see above) is unaffected by the presence of stannous chloride.

Robinson's theory of the Fischer synthesis postulates an ortho-benzidine conversion, thus:-

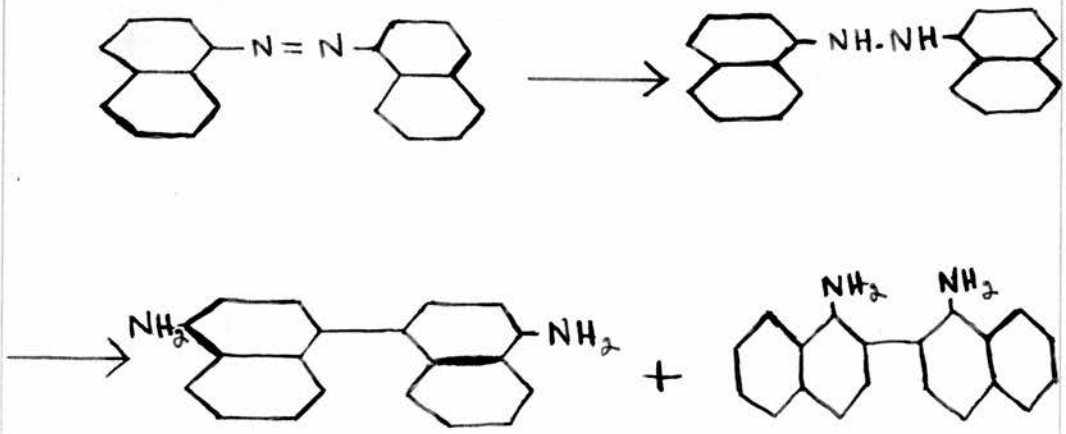


Considerable support for this theory may be adduced:-

For each stage in the scheme well-known analogies can be cited. Stage (1), the trans-:formation from enimic to enamic form, is analogous to the ketone-enol isomerisation, and indeed involves such a change in the ketone portion of the hydrazone. Therefore, if this theory were correct, it should be easier to make indoles from the hydrazones of easily enolisable ketones than from those of diffi-:cultly enolisable ones. That this deduction is in accordance with experience is supported by the fact that phenylacetaldehyde-phenylhydrazone is easily converted into β-phenyl indole by boiling with alcoholic hydrochloric acid, (Fischer and Schmitt, Ber./

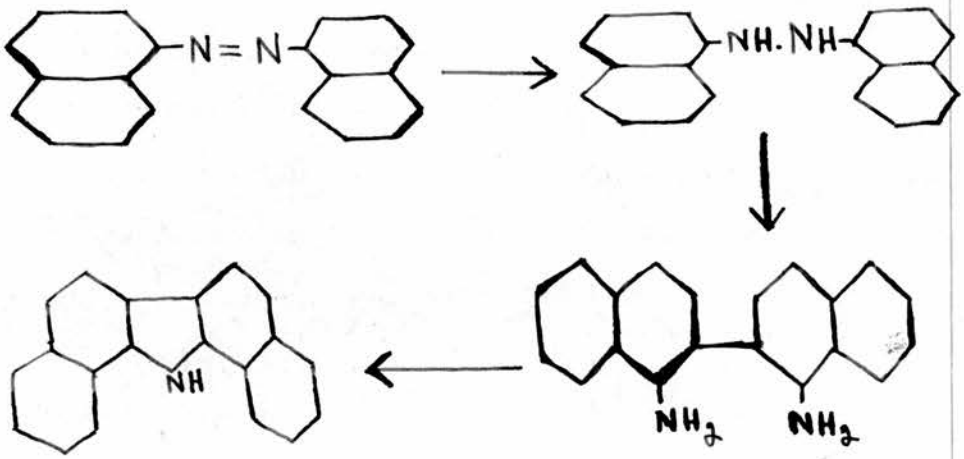
Ber., 1888, 21, 1072), whereas acetophenone-phenylhydrazone is only converted into α-phenyl indole on fusing with zinc chloride at 180° (Fischer, Ann., 1886, 236, 133). This, on Robinson's theory, would be attributed to the fact that acetophenone is not easily enolisable whereas phenylacetaldehyde is, as is shown by the fact that only the latter gives an acetyl derivative on boiling with acetic anhydride (Semmler, Ber., 1909, 42, 584).

The ortho-benzidine conversion postulated in stage (2) is a well-known transformation, being especially noted in the naphthalene series. For example, reduction of α-azonaphthalene with stannous chloride and hydrochloric acid yields naphthidine and dinaphthyline, these two substances being formed, under the action of the acid, by para-benzidine and ortho-benzidine conversions respectively from the primary product, α-hydrazonaphthalene. (Nietski and Goll, Ber., 1885, 18, 3252).

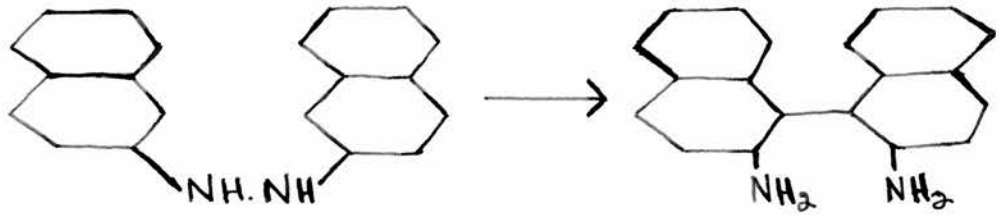


Naphthidine Dinaphthyline.

Incidentally, it is to be noted that dinaphthyline, on boiling with hydrochloric acid, yields dinaphthacarbazole (ibid.), so that the whole process of formation of this latter substance from α-azonaphthalene follows precisely the course postulated by Robinson as occurring in the Fischer indole synthesis.



A second example of an ortho-benzidine conversion is the formation of 2:2'-diamino-1:1'-dinaphthyl from β-hydrazonaphthalene (Meisenheimer and Witte, Ber., 1903, 36, 4161).

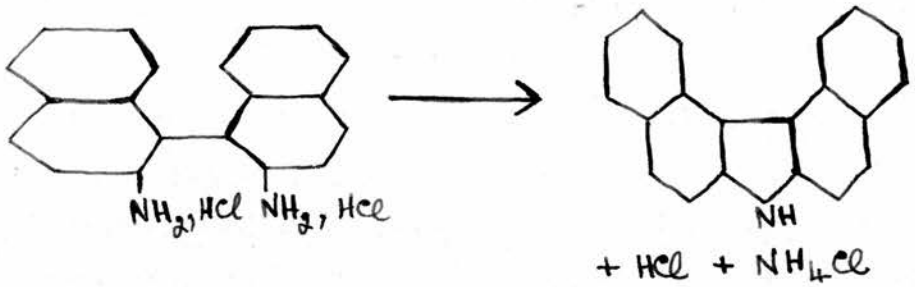


β-hydrazonaphthalene

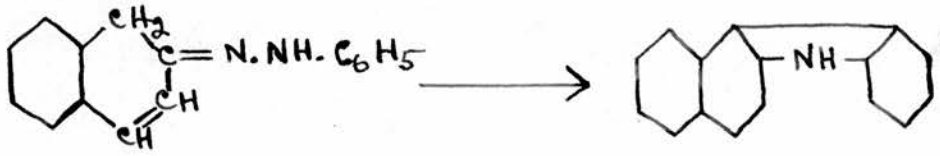
2:2'-diamino-1:1'-dinaphthyl

This diamine also can be converted into a carbazole in the usual way by loss of ammonia, on fusing/

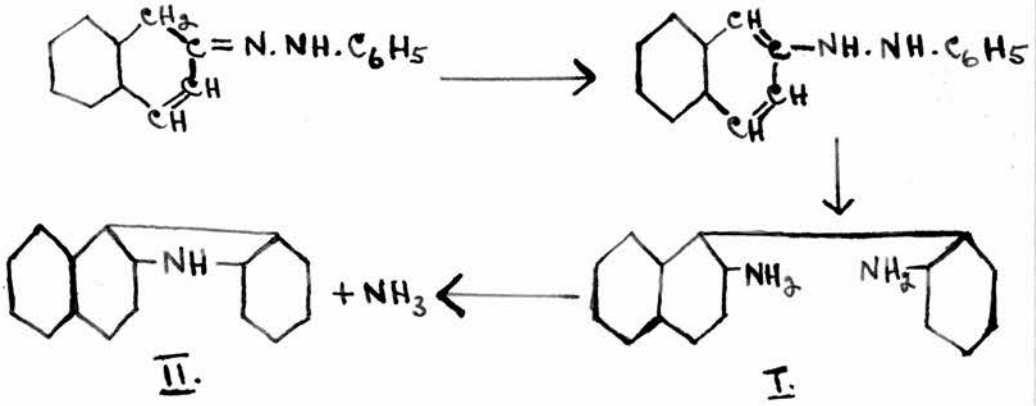
fusing the hydrochloride at 250° (ibid.).



Japp and Maitland (J.C.S., 1903, 83, 267) have prepared carbazoles by heating phenols with phenylhydrazine and phenylhydrazine hydrochloride. The authors consider that the phenols react in tautomeric keto forms to give hydrazones, which then undergo an ordinary Fischer reaction, thus:-

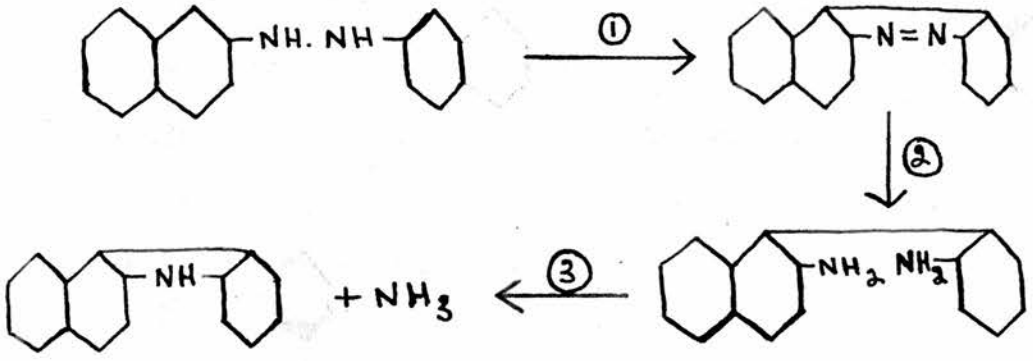


In Robinson's opinion this habit of referring the reactions of phenols to their keto modifications is a retrograde step, and in any case, even if such a hydrazone were formed, the next step would, he opines, be the production of a hydrazine, which would then undergo an ortho-benzidine transformation followed by loss of ammonia.



Evidence supporting this view of the reaction has been supplied since then by Fuchs and Niszel (Ber., 1927, 60, 209), who have prepared the carbazole II, by the action of phenylhydrazine sodium bisulphite on β-naphthol, and have isolated the diamine I from the reaction mixture. They have also shown that this diamine is converted, in excellent yield, into the carbazole II, by the action of sulphur dioxide.

Unfortunately, the yield of diamine was only 5% so that the experiment is open to the objection, actually made by Neber, Knöller, Herbst and Trissler (Ann., 1929, 471, 113) that this substance is not an intermediate product of the main reaction but a product of some secondary reaction such as the following:-



Stage (1) is represented as being analogous to the formation of β-azonaphthalene by reduction of β-nitro-naphthalene (Meisenheimer and Witte, Ber., 1903, 36, 4153). Presumably, in Neber's scheme, the oxidation in stage (1) will be effected by the phenylhydrazine

C_6H_5./

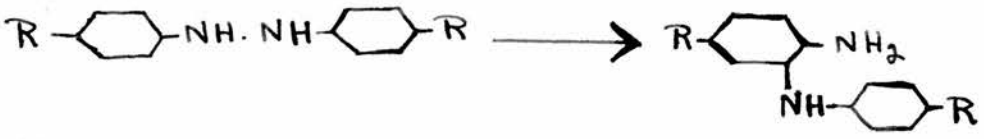
$$C_6H_5.NH.NH_2 + 2[H] \longrightarrow C_6H_5.NH_2 + NH_3$$

or by the reaction involved in stage (2).

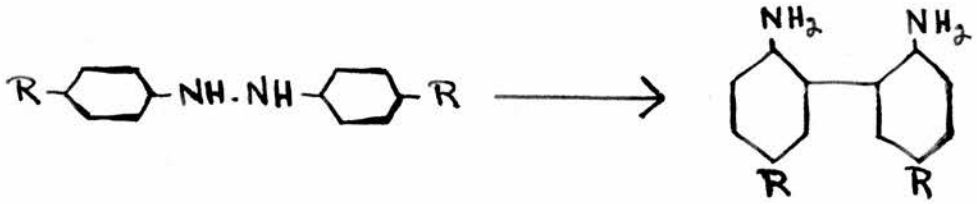
Stages (2) and (3), of course, represent well-known general reactions - disruptive hydrogenation of the azo-group, and carbazole formation from an O-O'-diamino-dinaphthyl.

The validity of Neber's objection, however, is open to question, and his alternative explanation of the production of the diamine I does not seem very probable.

The chief criticism levelled at Robinson's theory is that all well-established benzidine conversions take place in the para sense unless the para position is blocked by a substituent - which is not generally the case in Fischer syntheses. Even in cases where such blocking does occur and the blocking substituent is not eliminated to allow of a para conversion, the usual transformation is an ortho-semidine one



rather than an ortho-benzidine one



Hollins therefore contends that if an ortho-benzidine/

ortho-benzidine rearrangement does take place, at least part of the hydrazone should undergo the more usual para conversion. There is no evidence of this, although as Robinson points out, these products even if formed, would, on account of their great reactivity, be obtained only as tars—and a certain amount of tarring always takes place in a zinc chloride fusion.

A complete answer to this type of objection has, however, been put forward by Robinson in the shape of a general theory of the benzidine rearrangement. This and its application to the Fischer synthesis is shown below:-

If a molecule of the form A-b-c-D, in which A and D may be any radicles and b and c atoms capable of assuming a higher valency by salt formation, absorbs energy and becomes "activated", this is equivalent to partial dissociation and to the development of partial valencies on b and c, thus:-

(The acid is omitted for simplicity)

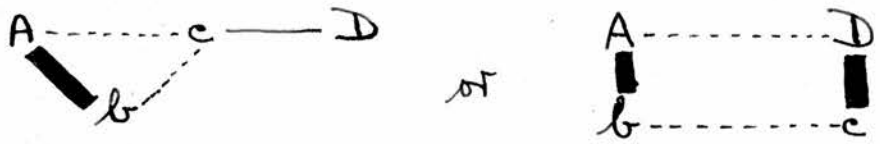
If A and/or D contains unsaturated groups, conjugation may occur with shift of the partial valencies to A and/or D.

E.g. 

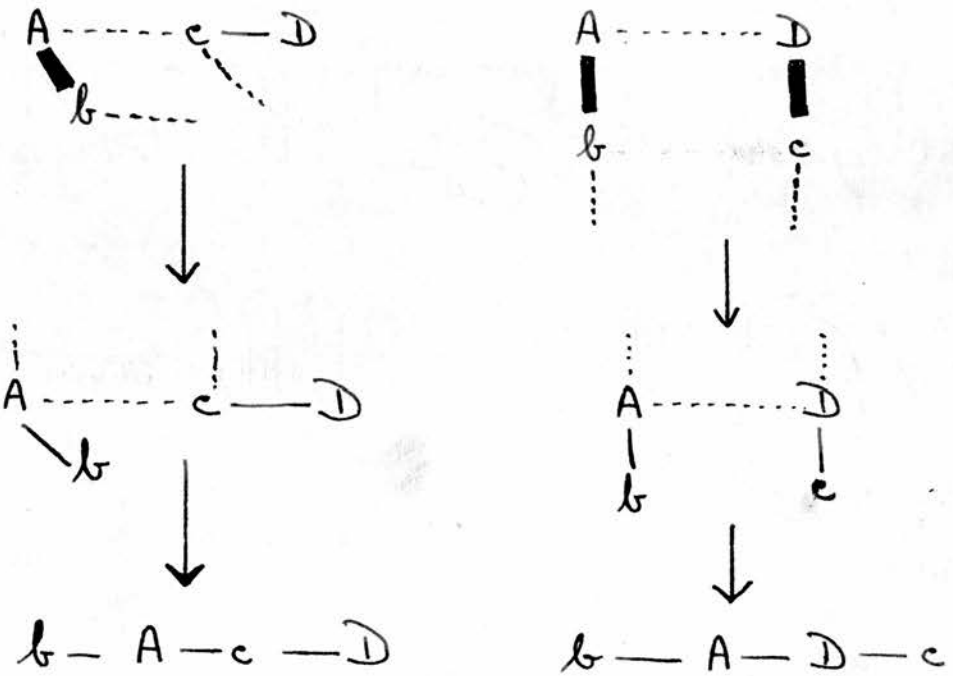
(A thickened line ▬ represents a normal valency plus a partial valency.)

Ring/

Ring formation of the partial valencies may now occur.



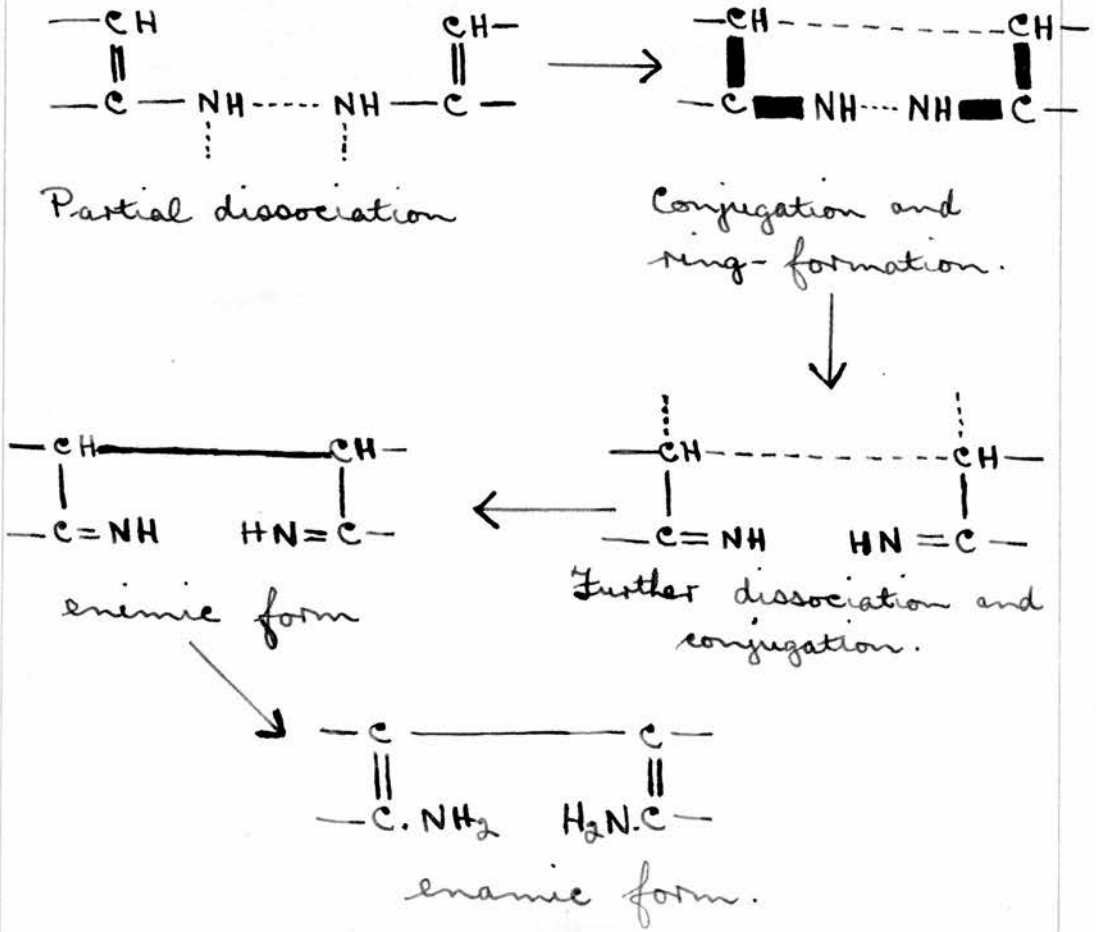
If now the whole process of energy absorption, development of partial valencies and conjugation occurs again, the result is as follows:-



The change A—b—c—D to b—A—c—D represents the semidine transformation, and the change A—b—c—D to b—A—D— c represents the benzidine rearrangement.

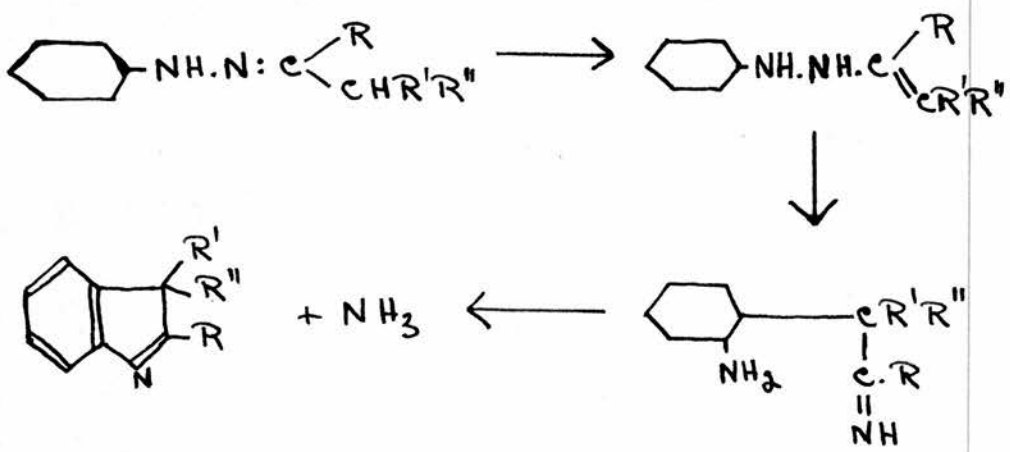
No assumptions have been made as to which portions of the radicles A and D have become conjugated, so that each may represent either an ortho or a para conversion, the point at which conjugation actually occurs being determined by other considerations.

In the case of the Fischer fusion, the most reactive group in the unsaturated hydrazine $C_6H_5.NR_1.NH.CR_2{:}\overset{*}{C}HR_3$, supposed by Robinson to be formed as a first step, is the unsaturated aliphatic group $-CR_2{:}\overset{*}{C}HR_3$. The initial partial valencies will therefore be formed there. After conjugation has occurred, one partial valency is left on the carbon atom marked with an asterisk (*), and the second one somewhere in the conjugated system of the benzene ring. Now for steric reasons it is obvious that ring formation between these two partial valencies can only occur if the second partial valency is on the carbon atom in the ortho position in the benzene ring. Thus the only possible conversion on this theory is the ortho-benzidine one.



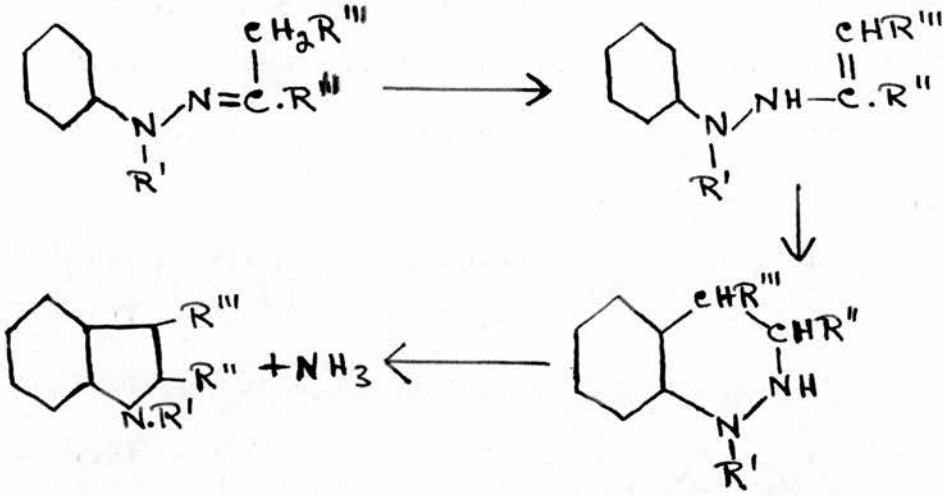
It is further pointed out by Robinson that "the necessary conditions for a Fischer synthesis, namely an acid reagent and a high temperature", are precisely the conditions which would favour each of his postulated stages if considered separately. Moreover, each stage is more basic than its predecessor, a generally observed phenomenon in intramolecular transformations brought about by an acid reagent. The loss of basicity at the last stage is due to an accident, namely ring-formation.

One fact quoted by Hollins in support of Reddelien's theory is the production of indolenines by Fischer fusion of hydrazones of the form $C_6H_5.NH.N:CR.CHR'R''$ (See page 130). This is easily explained on Reddelien's theory but it can also be explained by Robinson as follows:-



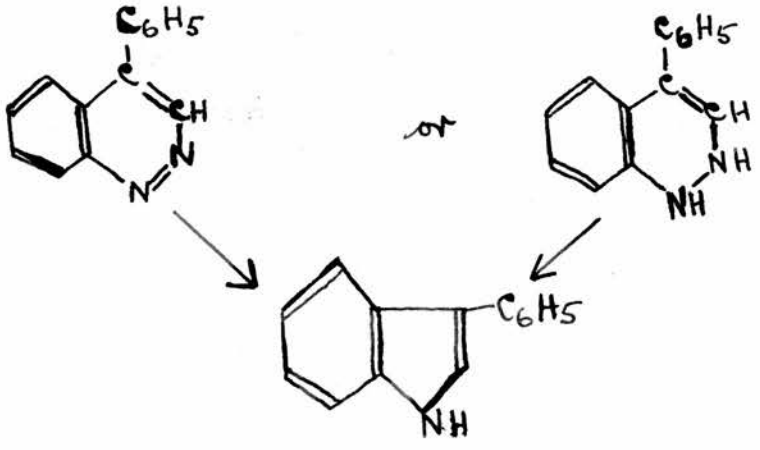
In a paper by Neber, Knöller, Herbst and Trissler (Ann., 1929, 471, 113) another theory is advanced to replace the Robinson mechanism, which the authors are unable to accept because of the above-mentioned objection concerning the formation of ortho-/

ortho-benzidine instead of para-benzidine conversion products. This new theory postulates isomerisation of the hydrazone to an unsaturated hydrazine, as in Robinson's theory, followed by ring closure and production of a tetra-hydrocinnoline derivative, which then splits out ammonia to form the indole.

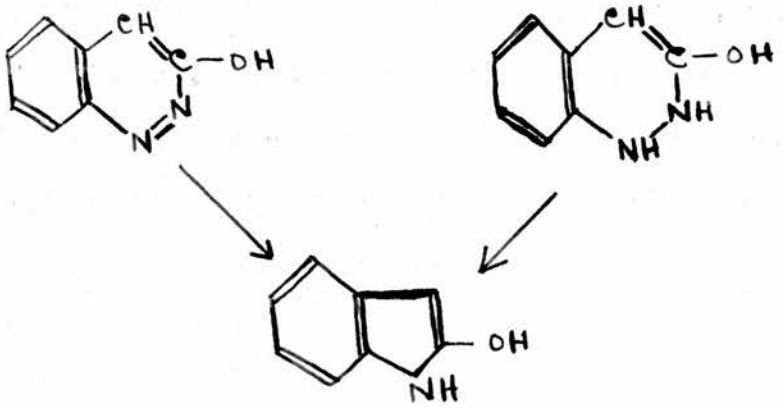


The authors produce evidence both for and against this mechanism, and finally conclude that neither their own theory nor that of Robinson satisfactorily explains the Fischer synthesis.

The original basis of the latter theory was the observation that 4-phenyl-cinnoline and its dihydro- derivative both gave 3-phenyl indole by reduction in acid solution.



Similarly, acid reduction of 3-hydroxy-cinnoline or its dihydro-derivative gave oxindole.



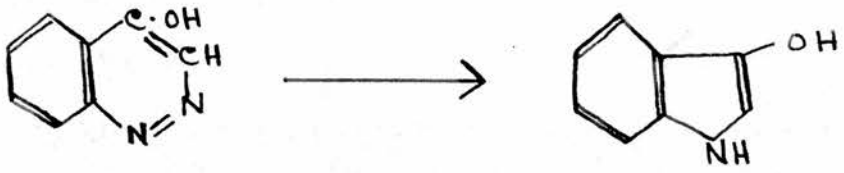
It seemed probable that these syntheses proceeded via the tetrahydrocinnoline derivatives

Since these derivatives, however, appeared to be converted immediately, in presence of acid, into the corresponding indoles, it was found impossible to isolate them.

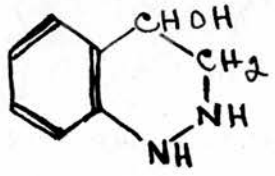
Some cases were therefore investigated in which it was considered probable, that in view of the heavily substituted nature of the tetrahydro-:cinnoline formed, the completion of the process by formation of an indole derivative would be impeded, and the intermediate compound found to be isolable. In no case was success attained, as either the indole was formed at once or else the reaction took an entirely different course yielding neither the intermediate/

intermediate product nor the indole expected.

It was then found that whereas reduction of 3-hydroxycinnoline by boiling hydriodic acid gave oxindole, a similar reduction of 4-hydroxycinnoline yielded chiefly a resin (which probably arose from the action of hydriodic acid on the sensitive indoxyl presumably formed).



From this resin, however, was isolated a substance which was identified as the hydriodide of 4-hydroxy-tetrahydrocinnoline.



This substance was found to be quite stable to boiling hydriodic acid.

Furthermore, 4-phenyl-tetrahydro-cinnoline was prepared and shown to be quite stable to boiling concentrated hydrochloric acid. Only a trace of indole was formed after boiling for a whole day.

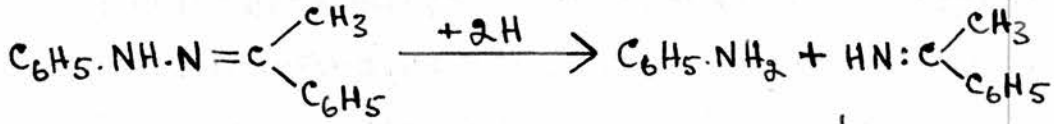
It was also found that 4-phenyl-tetrahydro-:cinnoline and 4-phenyl cinnoline were formed by heating 4-phenyl-dihydrocinnoline with hydrochloric acid in a sealed tube to 120°. This stability of the former product under conditions so favourable for indole formation made it almost certain that it could/

could not be an intermediate compound in the formation of 3-phenyl indole by the Fischer synthesis.

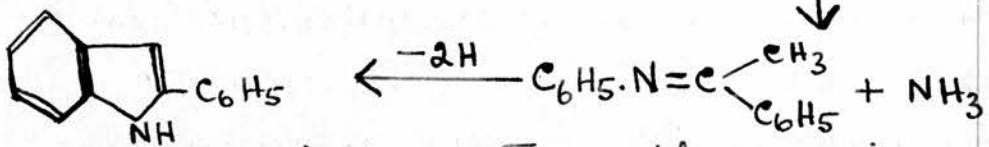
EXPERIMENTAL.

A. Disproof of Reddelien's Theory.

According to this theory the formation of α-phenyl indole from acetophenone-phenylhydrazone by the Fischer synthesis follows the course.

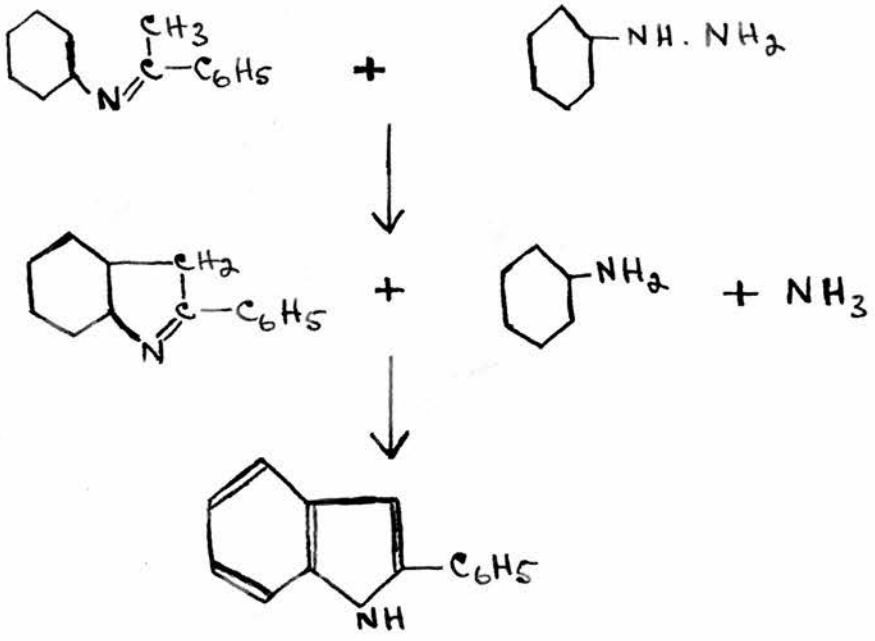


I. Acetophenone-phenylhydrazone

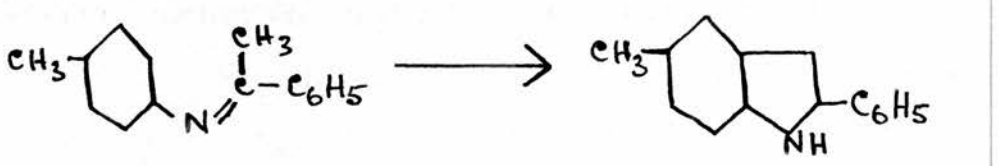


III. α-phenyl indole II. acetophenone-anil

This view is based on the observation that α-phenyl indole is also formed by fusing together at 250° acetophenone-anil (II.) with phenylhydrazine-zincichloride, a reaction which Reddelien interprets as an oxidation of the anil by the phenylhydrazine, by removal of two hydrogen atoms.



If this were correct, then fusion of acetophenone-p-tolil with phenylhydrazine-zincichloride should yield α-phenyl-p-toluindole, and employment of the o-tolil instead of the p-tolil should give α-phenyl-o-toluindole.



acetophenone-p-tolil α-phenyl-p-toluindole

This possibility was therefore investigated as follows. Acetophenone-p-tolil and acetophenone-o-tolil were prepared and each of them fused with phenylhydrazine-zincichloride, the indole formed being isolated and identified in each case.

Preparation of phenylhydrazine-zincichloride.

$(C_6H_5.NH.NH_2)_2$, $Zn\ Cl_2$.

Phenylhydrazine (14 gms.) and zinc chloride (9 gms.) were dissolved separately in absolute alcohol and the solutions mixed. A white precipitate formed almost immediately, and this was filtered off and dried. Yield theoretical (23 gms.).

Preparation of o- and p- Toluidine-zincichlorides.

$(CH_3.\ C_6H_4.NH_2)_2$, $Zn\ Cl_2$.

These were prepared exactly as above for phenylhydrazinezincichloride, using 13 gms. of toluidine and 8 gms. of zinc chloride. Yield almost theoretical (20 gms.).

Preparation of Acetophenone-p-tolil.

(Reddelien, Ann., 1912, 388, 165).

Acetophenone (20 gs.) and p-toluidine (25 gs.) were mixed in a nickel crucible which was then heated on an oil-bath to 160°. One gram of p-toluidine-zincichloride was now added and the temperature kept at 180° for 20 minutes. The melt was then allowed to cool.

The ketone and amine did not react to give the tolil until the catalyst (p-toluidinezincichloride) was added. On addition of the latter, a vigorous reaction commenced with evolution of steam and ammonia.

The cold melt was extracted with boiling chloroform, the chloroform removed by evaporation, and the oily residue distilled at atmospheric pressure, the fraction boiling below 240° being rejected. The tolil was then distilled at 182°-183° under 16 m.m. pressure. The yield obtained was 7 gms., representing 20% of the theoretical. In a second experiment a yield of 24% was obtained (9 gms. of tolil from 21 gms. of acetophenone).

The substance was obtained as a pale yellow oil, which did not solidify and which turned red on exposure to the air.

Preparation of Acetophenone-o-tolil.

Bogert and Herrera, J.A.C.S., 1923, (45),240.

Acetophenone (38 gms.), o-toluidine (49 gms.)

and/

and o-toluidine-zincichloride (2 gms.) were heated together at 180° for one hour, and the resultant tolil extracted in the same way as the para compound described above.

The tolil was collected at 184°-189° under 20 m.m. pressure. The yield obtained was 25 gms., or 43% of the theoretical.

The substance was obtained as a pale yellow oil, which solidified on standing to a yellow crystalline solid (plates) melting at 58°. (Bogert and Herrera's preparation did not solidify). The substance could not be recrystallised because of its extreme solubility in all the common solvents - alcohol, ether, benzene, petrol ether, chloroform, carbon disulphide, ethyl acetate, carbon tetrachloride, pyridine, acetic acid, etc.

The substance was insoluble in water but separated from aqueous alcohol as an oil.

Fusion of acetophenone-p-tolil with phenylhydrazine-zincichloride.

These two substances, 7 gms. of the former and 6 gms. of the latter, were heated together to 280° and kept at that temperature for a few minutes, until evolution of steam and ammonia ceased. The melt was then cooled, the brown uncharred residue boiled with chloroform, and the resultant solution filtered.

A dark blue strongly fluorescent filtrate was obtained, which was evaporated to dryness. The residue was recrystallised first from benzene and then from alcohol, a light-grey product being obtained which gave the pine-splint test and melted at 189° both alone and when mixed with an equal quantity of α-phenyl indole (m.p. 189°).

The substance was therefore α-phenyl indole and not α-phenyl-p-toluindole which melts at 216°. To make quite certain of this, the substance was converted into the isonitroso-compound. The product so obtained, after recrystallisation from amyl acetate, was found to melt at 280° either alone or mixed with 2-phenyl-3-isonitroso indole (m.p. 280°). The substance was not, therefore, the isonitroso compound of α-phenyl-p-toluindole, which melts at 273°.

Finally, the isonitroso-compound of the indole obtained in the above fusion was acetylated, and the product, after recrystallisation from ligroïn, found to melt at 117° either alone or mixed with 2-phenyl-3-acetyloximo-indolone (m.p. 117°). The corresponding derivative of α-phenyl-p-toluindole melts at 169·5°.

There was thus no doubt whatever that the indole obtained was α-phenyl indole and not α-phenyl-p-toluindole.

Fusion of acetophenone-o-tolil with phenylhydrazinezincichloride.

These two substances, 25 gms. of the former and 21 gms. of the latter, were heated together to 250°. After the evolution of ammonia had ceased, the fusion mixture was cooled and extracted, as described above, with chloroform. The residue left after evaporation of the latter was recrystallised twice from alcohol, and shown by melting-point and mixed melting-point to be α-phenyl indole (m.p. 189°) and not α-phenyl-o-toluindole (m.p. 117°).

Part of this indole was coupled with benzenediazonium chloride, and the product shown by melting-point and mixed melting-point (164°) to be the 3-benzeneazo derivative of α-phenyl indole, and not the corresponding derivative of α-phenyl-o-toluindole, which melts at 155°.

The other portion of the indole was converted into the isonitroso-compound. The product, when purified, was found to melt at 280°, either alone or mixed with the isonitroso-compound of α-phenyl indole (m.p. 280°). The isonitroso-compound of α-phenyl-o-toluindole melts at 244°. The isonitroso-compound of the indole formed in the fusion was next benzoylated, and the substance obtained shown by melting-point and mixed melting-point (153°) to be 2-phenyl-3-benzoyloximo-indolone (m.p. 153°) and not 2-phenyl-3-benzoyloximo-7-methyl indole (m.p. 163°).

To/

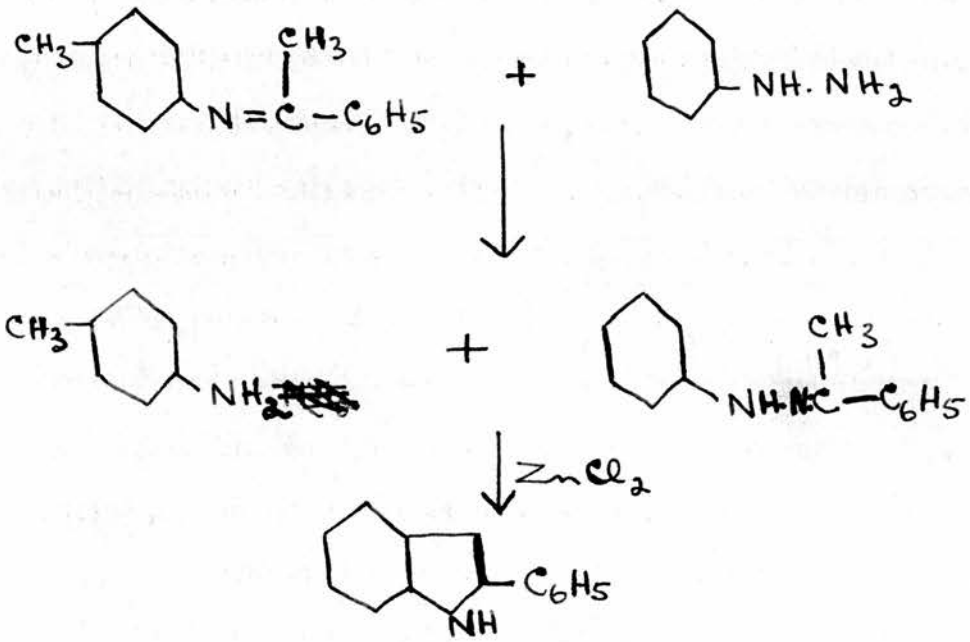
To make sure that no other indole had been formed, and lost during the purification process, the mother-liquors from the recrystallisations of the indole were collected together, evaporated to dryness, and the residues dissolved in glacial acetic acid. Powdered sodium nitrite was added, and the resultant red solution poured into water. A yellow precipitate was thrown down, and this was filtered off, washed with water, alcohol and ether, dried and recrystallised from amyl acetate. The substance obtained melted at 269° before recrystallisation and at 280° after recrystallisation, and was therefore 2-phenyl-3-isonitroso indole (m.p. 280°) and not 2-phenyl-3-isonitroso-7-methyl indole (m.p. 244°). As is shown by the melting-point before recrystall-:isation (269°), the latter compound could not have been present in the substance actually obtained, except, possibly, as a slight trace.

Finally, to place the matter beyond all doubt, the isonitroso-compound obtained from the mother-liquors was benzoylated, and the product shown by melting-point and mixed melting-point (153°) to be the 3-benzoyloximo-derivative of α-phenyl indole (m.p. 153°) and not that of α-phenyl-o-toluindole (m.p. 163°).

This observed production of α-phenyl indole

by/

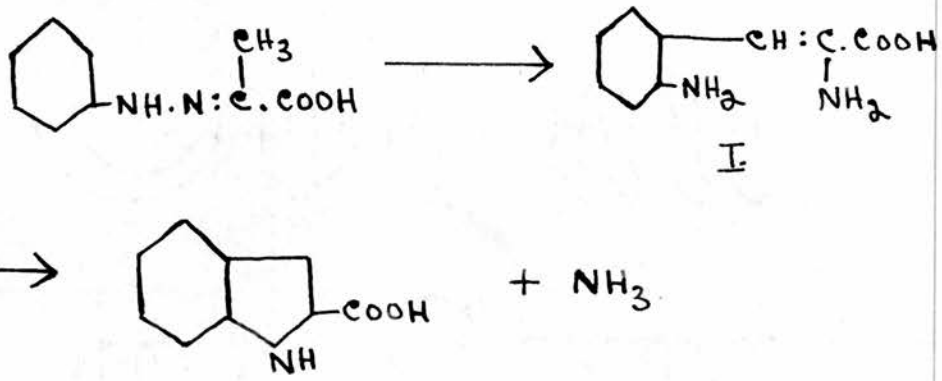
by fusing phenylhydrazine-zincichloride with either acetophenone-p-tolil or acetophenone-o-tolil shows clearly that Reddelien's view of the reaction is erroneous, and that what probably occurs is a double decomposition between the tolil (or anil) and the hydrazine, with production of a hydrazone. The latter, under the influence of the zinc chloride, is immediately converted into an indole derivative, exactly as in a Fischer fusion.



Consequently, Reddelien's mechanism of the Fischer indole synthesis also becomes untenable, since it is based on the view that the hydrazone proceeds to the indole via an anil, whereas actually it appears that the anil can only be converted to the indole via the hydrazone.

Attempts to test Robinson's Theory of Indole Formation.

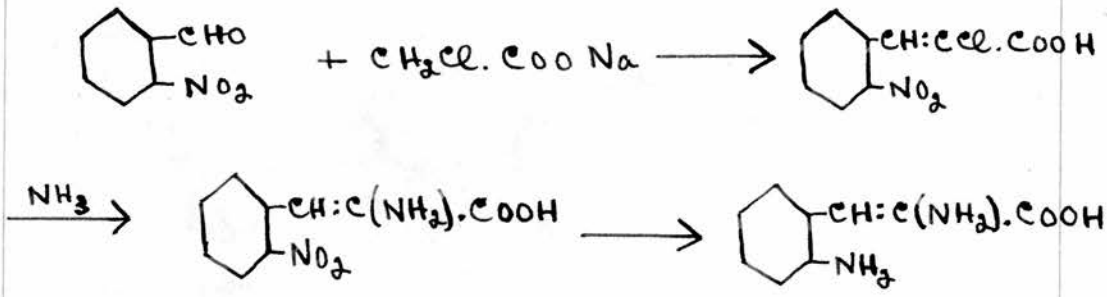
A direct attack on the subject was decided upon by attempting to synthesise one of the intermediate compounds postulated by Robinson as being formed during the Fischer synthesis of a suitable indole, the one chosen for this purpose being indole-2-carboxylic acid.



I.

First attempted synthesis of the intermediate compound I.

The following scheme was envisaged, the first stage being an ordinary Perkin reaction:-



The only known method of preparing α-chloro-o-nitro-cinnamic acid (Naar, Ber., 1891, 24, 251) is an extremely round about one, so that the following method/

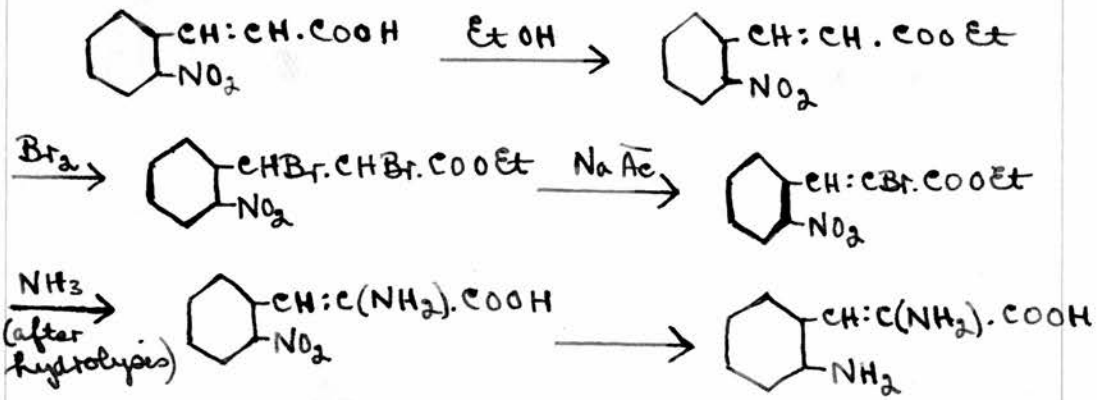
method of preparation was tried:-

o-Nitro-benzaldehyde (10 g.) sodium chloracetate (8 g.) and acetic anhydride (15 g.) were boiled together for seven hours, and the product poured into water. After neutralising with sodium carbonate, filtering from tar, and acidifying the filtrate with concentrated hydrochloric acid, the precipitate obtained was recrystallised from water, and found to melt at 238°. The substance was thus o-nitro-cinnamic acid and not α-chloro-o-nitro-cinnamic acid (m.p. 201°-202°).

The preparation was therefore repeated, the acetic anhydride (15 g.) being replaced by chloracetic anhydride (20 g.). The product now obtained from the reaction, however, was an impure dark brown resinous substance, which melted with decomposition at 137°. This was not the desired compound, and appeared to be a condensation product of chloracetic anhydride with itself. The method was therefore abandoned, and a different scheme adopted.

Second attempt to prepare the intermediate compound I.

The following scheme was tried.



(1) Esterification of o-Nitro-Cinnamic Acid.

(a) Fischer-Speier method.

50 g. o-nitro-cinnamic acid.

300 c.c. absolute alcohol, saturated with dry hydrochloric acid gas.

The mixture was boiled under reflux for two hours, and allowed to cool, when the ester separated as a yellow substance melting at 38°-42°, the yield being 21 g.. The pure ester melts at 42°-44°, but the product obtained was not purified further, as this led to excessive loss.

A second crop amounting to 4 g. was obtained, while the filtrate, on pouring into water, gave a further 14·5 g. of fairly pure ester, so that the total yield, 39·5 g., represented 69% of the theoretical of crude product.

(b) Thionyl chloride method.

This was undertaken with a view to improving the yield.

10 g. o-nitro-cinnamic acid.

20 g. thionyl chloride.

100 c.c. absolute alcohol.

The thionyl chloride and the acid were heated under reflux on the steam-bath for four hours. Excess of the former reagent was distilled off in vacuo on the water-bath, the absolute alcohol added, and the mixture boiled for two hours under reflux. Excess alcohol was distilled off in vacuo, and the dark-red residue removed and recrystallised from this solvent.

The ester was obtained as a light yellow solid, melting at 35°-42°, the yield of 5 g. only representing 43% of the theoretical.

It is evident, therefore, that in the present case the thionyl chloride method gives a poorer yield.

(2) Preparation of α-β-Dibromo-β-(2-nitro-phenyl)-Propionic Ester.

Müller, Ann., 1882, 212, 129.

26 g. o-nitro-cinnamic ester.

400 c.c. dry carbon disulphide.

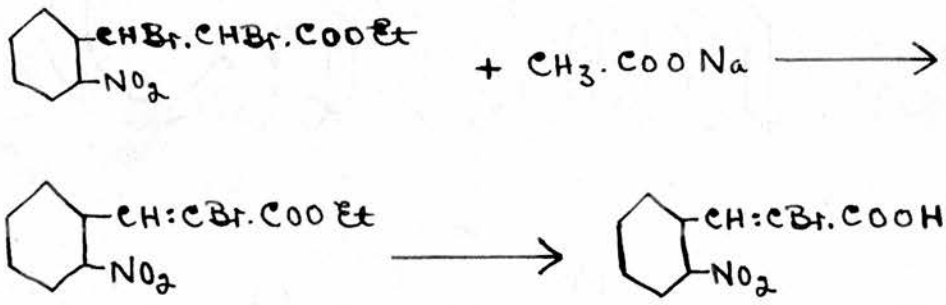
20 g. bromine.

The ester was dissolved in the carbon disulphide, and the solution boiled under reflux, while the bromine was added slowly from a dropping-funnel/

dropping-funnel over a period of one to three hours. When all the bromine had been added, the mixture was boiled until almost colourless. Part of the carbon disulphide was distilled off, and the residue allowed to crystallise, when the dibromo-compound separated as yellow crystals, the yield being 37 g., or 80% of the theoretical.

(3) Preparation of α-Bromo-o-nitro-Cinnamic Acid.

Reich and Chang, Helv., 1920, 3, 235.



37 g. α-β-dibromo-β-(2-nitro-phenyl) propionic ester.

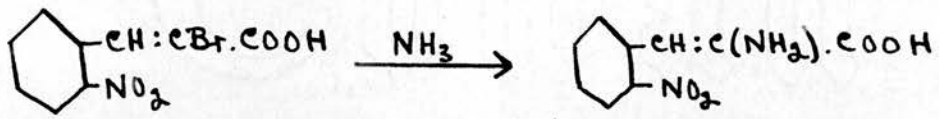
8·3 g. freshly fused, anhydrous, sodium acetate.

The two reactants were dissolved in absolute alcohol and the mixture boiled under reflux for two hours. The alcohol was then distilled off, water added, and the product extracted with ether. After evaporation of the ether, the ester was left as an oil (29 g.), which was hydrolysed by dissolving one part of it in a mixture of glacial acetic acid (5 parts), water (1 part) and concentrated sulphuric acid (1 part), and heating on the steam-bath until a sample/

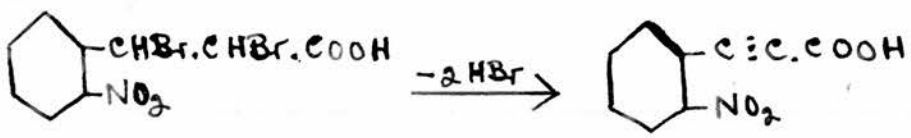
sample, poured into water, gave a precipitate completely soluble in ammonia (5 hours heating).

The mixture was poured into water, and the precipitated acid filtered off and recrystallised from alcohol, the yield obtained (15 g.) being 57% of the theoretical.

(4) Attempted preparation of α-Amino-o-nitro-cinnamic acid.



Two difficulties were associated with this stage of the synthesis, firstly the de-activation of the bromine atom by the adjacent double bond, and secondly the possibility of removing HBr from the starting product instead of replacing -Br by $-NH_2$. The first difficulty, it was hoped, would be adequately met by the presence of the activating carboxyl group, a consideration which had originally decided the choice of the particular indole to be investigated in this section. As for the second difficulty, it was known that sodium hydroxide removed hydrobromic acid fairly readily from α-β-dibromo-β-(2-nitro-phenyl)-propionic acid with production of 2-nitro-phenyl-propiolic acid,



a reaction which probably proceeded via the mono-bromo acid above, but it was hoped that ammonia, being a much feebler base, would not react so rapidly in this manner, and so permit of the desired replacement of -Br by $-NH_2$.

It was found, however, as a result of several experiments carried out under different conditions, that the product obtained was o-nitrophenyl-propiolic acid, m.p. 160·5° (% N, 7·3; whereas α-amino-o-nitro-cinnamic acid requires % N, 13·5).

To determine whether this difficulty could be avoided by the use of a lower reaction temperature, the following experiment was carried out:-

α-Bromo-o-nitro-cinnamic acid (0·5 g.) was placed with 50 c.c. of concentrated ammonia in a tightly stoppered lemonade bottle, and the latter kept for three and a half days in a thermostat at 50°. On opening the bottle and boiling off the excess ammonia, a neutral solution was obtained which was extracted with ether. The ether extract, on evaporating to dryness, gave a brown amorphous powder (0·033 g.) melting at 97°-101°.

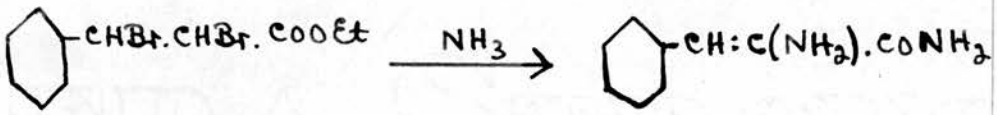
The aqueous layer, on acidifying with hydrochloric acid, gave a light brown precipitate, which, on filtering off and drying, melted with decomposition at 205°. The yield obtained was 0·055 g.. The substance was acidic, contained no halogen (copper wire test), decolourised neutral permanganate, and changed in colour on long exposure /

exposure to the air. It did not give the ninhydrin reaction, however, and contained only 8·4% of nitrogen (three determinations by the micro-Dumas method gave 8·3%, 8·4% and 8·6%).

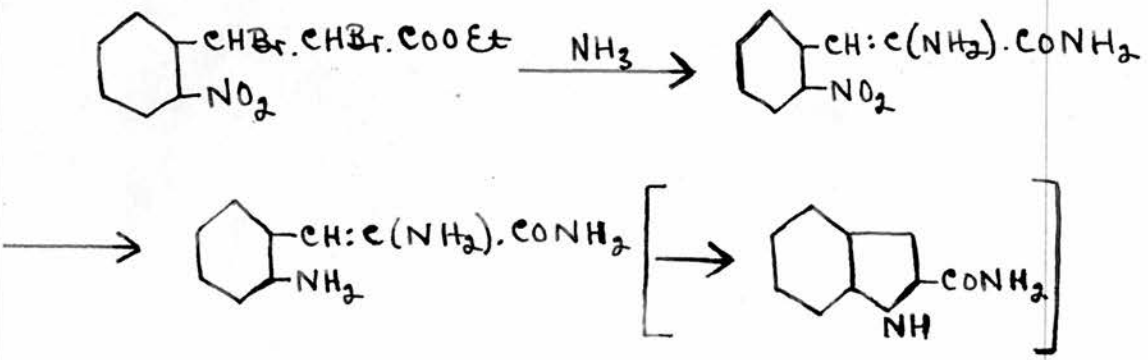
Beyond the obvious conclusion that this substance was not the compound sought, and that it appeared to be an unsaturated nitro-acid, no suggestion as to its nature is advanced, and the subject was not pursued further.

Third attempt to test Robinson's theory.

An examination of the literature revealed the fact that, when heated to 45° with concentrated ammonia for three days, dibromo-cinnamic ester was converted into α-amino-cinnamic acid amide:- (Baucke, Recueil Travaux., 1896, 15, 131).



The following scheme therefore suggested itself:



(a) Preparation of α-Amino-o-nitro-cinnamic acid amide.

α-β-Dibromo-/

α-β-Dibromo-β-(2-nitro-phenyl)-propionic ester, the preparation of which is described above (page 161), was mixed with concentrated ammonia in a tightly stoppered lemonade bottle, which was placed in a thermostat at 50°. After two days a crystalline product had deposited on the bottom of the bottle, but on the third day most of this had gone into solution and the supernatant liquid become dark.

The bottle was therefore opened, the excess ammonia boiled off, and the solution decolourised with animal charcoal and filtered. The filtrate deposited yellow crystals on cooling (3·44 g. from 20 g. of dibromo ester). These were very soluble in alcohol, but sparingly soluble in benzene, ligroïn, acetone and chloroform, even on boiling. It was also observed that the substance decomposed gradually on prolonged boiling with water, so that it could not be obtained pure by recrystallisation from this solvent.

For analysis, the compound was recrystallised from ligroïn, from which it separated as a white flocculent precipitate of melting-point 221°.

Nitrogen analysis:- (Micro-Dumas method)

Found	N 20·5%
Calculated for α-amino-o-nitro-cinnamic acid amide	N 20·3%

(b) Reduction of α-Amino-o-nitro-cinnamic acid amide.

The method adopted was that used for the analogous reduction of o-nitro-cinnamic acid to o-amino-cinnamic acid. (Gabriel, Ber., 1882, 15, 2294./

2294.), in order to avoid the possibility of the double bond being reduced at the same time. It was not expected that the o-amino-compound would be isolated, as it was almost certain that this would pass, directly on formation, by elimination of ammonia between the amino-groups, into indole-2-carboxylic acid amide (assuming that Robinson's mechanism of the Fischer indole synthesis is correct).

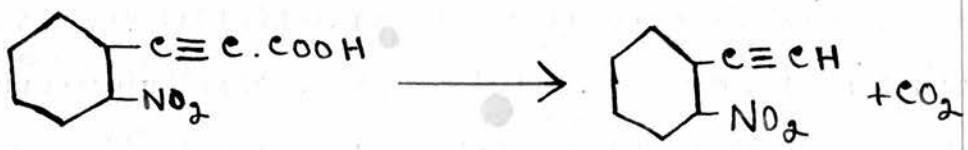
α-Amino-o-nitro-cinnamic acid amide (1 g.) was dissolved in 30 c.c. of hot alcohol and added to a boiling mixture of ferrous sulphate crystals (10 g.) and concentrated ammonia (100 c.c.). The whole was boiled under reflux for 15 minutes, cooled, and acidified with concentrated hydrochloric acid. After filtering from a small quantity of insoluble matter, the mixture was extracted with ether. The resultant extract (reddish in colour), showed a strong purple fluorescence such as is characteristic of many indoles, but evaporation to dryness left only a minute residue, too small for proper examination. This was therefore dissolved in 2 c.c. of alcohol and treated with Ehrlich's reagent, but no characteristic colouration was obtained.

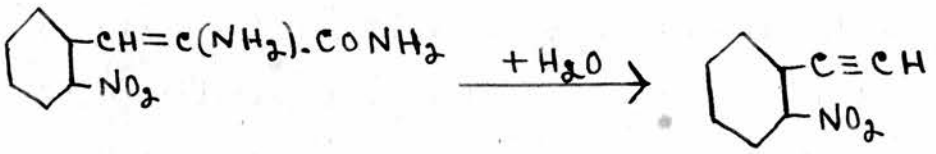
The experiment was then repeated, the reducing mixture being boiled for one hour. The ether extract now obtained showed a much stronger purple fluorescence, but the residue left on evaporation still failed to give Ehrlich's test and was too small in quantity for any other examination.

In/

In a previous experiment, the method adopted had been to filter off the ferrous and ferric hydroxides from the reaction product and test residue and filtrate separately for the presence of either the indole or the amino-acid. Neither an ether extract of the filtrate nor an alcoholic extract of the residue, however, contained either of these, the latter containing no alcohol-soluble material whatever.

In these circumstances the experiments undertaken were inconclusive, as neither the starting material nor any product of the reaction was obtained. While this must remain surprising, it is to be noted that the former was a somewhat labile substance, which decomposed fairly readily on prolonged boiling with water, so that it is not improbable that the loss of material may have been due to this cause. It was noted that a peculiarly penetrating and unpleasant (not indole-like) odour always manifested itself during these reductions, and also previously during the preparation of the nitro-amide. This clung tenaciously to the products examined, and may possibly have been due to the evil-smelling o-nitro-phenyl-acetylene (or to o-amino-phenyl-acetylene). This substance is volatile in steam and would be easily lost, while the possibility of its formation is at once apparent when it is remembered that it is readily formed by loss of carbon dioxide from o-nitro-phenyl-propiolic acid.



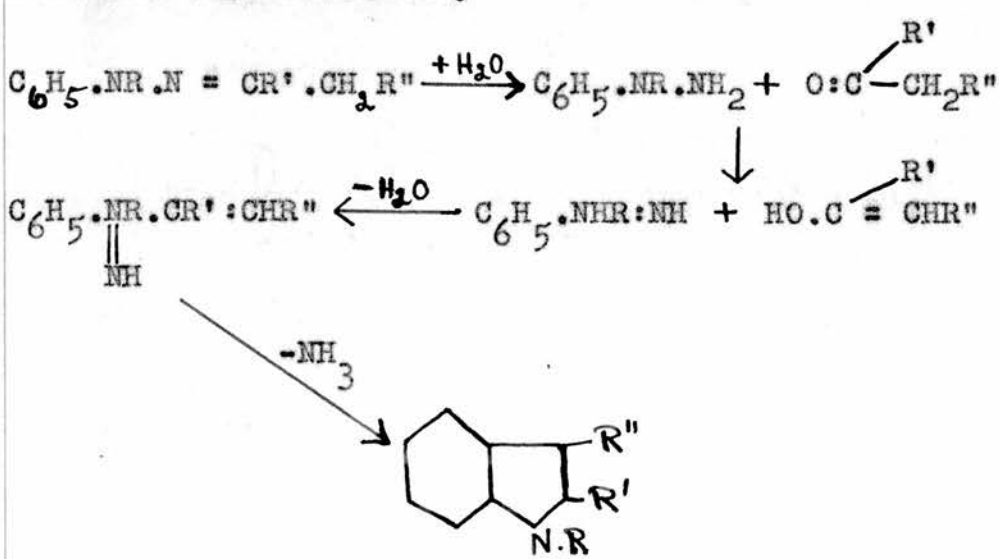


$+ CO_2 + 2 NH_3$

DISCUSSION.

To the views on the Fischer synthesis found in the literature and discussed in the introduction to this part, the following observations are now appended.

Firstly, with regard to the theory of Bamberger and Landau, which has been criticised by both Robinson and Hollins (J.C.S., 1924, 125, 827; J.A.C.S., 1922, 44, 1598) on the grounds that it does not explain the production of N- substituted indoles from hydrazones of the type $C_6H_5.NR.N:CR'.CH_2R''$, the following modified mechanism may be advanced to overcome this difficulty:-



This scheme has the advantage, in comparison with the original, that it gives rise to an indole derivative directly, instead of via an indolenine, but at the same time the replacement of the well-established reaction

$$>CO + H_2N- \longrightarrow >C=N- + H_2O$$

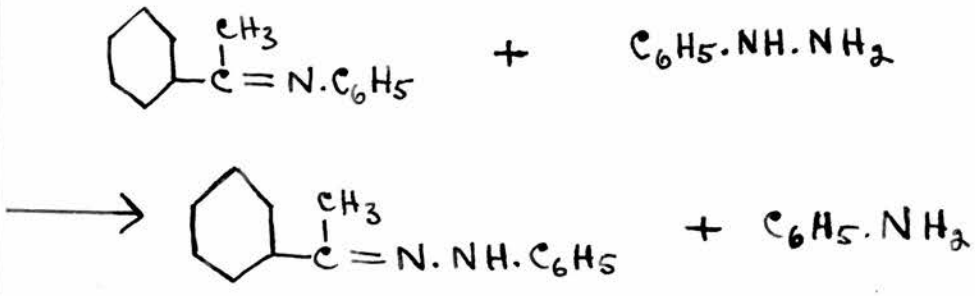
by/

by the less likely one

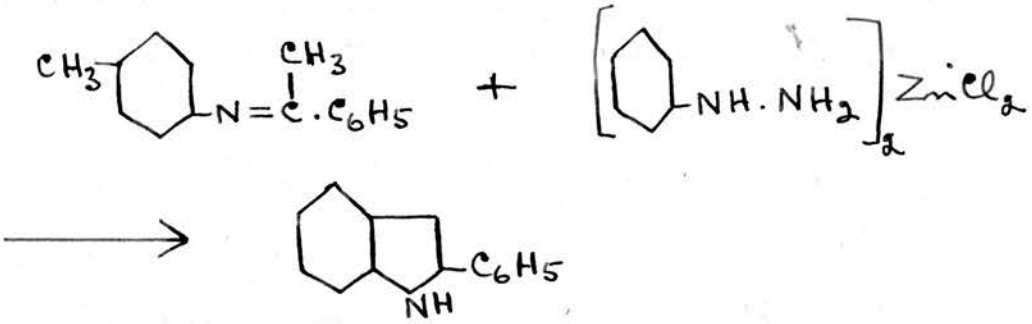
must be considered a weakness in the theory. This mechanism, however, in view of the other objections previously discussed, is not considered a very likely one, and is not therefore seriously advanced here.

The theory of Cohn may be dismissed without further discussion, but that of Reddelien deserves more mention. The paper of Bodforss (Ber., 1912, 45, 2150), to which reference has already been made, was unfortunately overlooked until the present investigation was well in hand, so that the disproof of Reddelien's theory described above is partly a repetition of some of Bodforss' work. At the same time, however, it must be noted that the latter work was so unsatisfactory in many respects that it had to be repeated, since the evidence submitted carries no weight.

Apart from the important supplementary observation that acetophenone-anil undergoes double decomposition with phenylhydrazine at 60°, with production of acetophenone-phenylhydrazone and aniline,



Bodforss' "disproof" of Reddelien's theory is based solely on the fact that the indole obtained by fusing together phenylhydrazine-zincichloride and acetophenone-p-tolil was α-phenyl-indole, and not α-phenyl-p-toluindole as required by this theory.

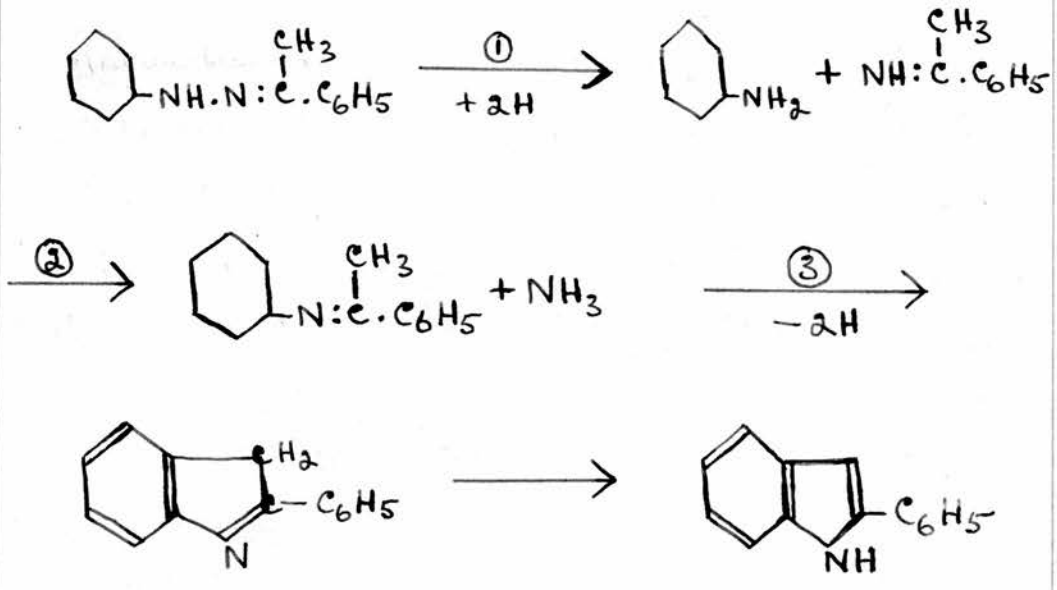


Bodforss, however, obtained a yield of "pure α-phenyl indole" which represents 136% of the theoretical (m.p. observed, 188°-189°), and "confirmed" his identification of the latter by converting it into the "nitroso-compound", which he found to melt at 161°-162° (with decomposition). It is evident, therefore, that the yield of indole can be explained on the assumption that the substance actually obtained was highly impure α-phenyl-p-toluindole (m.p. 216°). In addition, the quoted melting-point of the "nitroso-compound" is 100° lower than the then accepted value (258° (d.)). If this is an error it has never been corrected, and has led the compilers of Centralblatt to list the substance as a new compound, N-nitroso-α-phenyl indole. In any case, we can scarcely accept the melting-point of 261°-262° (d.) as evidence that the substance obtained was "nitroso"-α-phenyl-indole (accepted m.p. 258° (d.)) and not "nitroso"-α-phenyl-p-toluindole (accepted/

(accepted m.p. 262° (d.)). Finally, as it has now been shown (this thesis), that the melting-points of the latter two substances are actually 280° (d.) and 273° (d.), it is obvious that the quoted evidence of the "nitroso-compound" is also valueless.

It will therefore be apparent that the repetition of Bodforss' work was necessary.

One objection to the Reddelien theory put forward by Bodforss is to the effect that, in some cases, the yield of indole obtained is quantitative, which would not be so if there was a preliminary decomposition of part of the hydrazone. Obviously, of course, since the hydrogen thus obtained is recovered, and used over and over again, only a single molecule of hydrazone (in theory) or only a minute fraction of the total number of molecules (in practice) would require to be decomposed, the resultant defection from a 100% yield of indole being indemonstrable experimentally. Further, it will be seen, if Reddelien's paper is correctly read, that this hydrogen is only required to initiate the reaction, the latter being subsequently carried on by the mutually compensating oxidation and reduction reactions (3) and (1).



A second objection of Bodforss is that the red colour developed during the course of the reaction is only transitory, and cannot therefore be cited as evidence of a preliminary decomposition of the hydrazone. Equally obviously, of course, there is no necessity for the coloured decomposition products to remain. They may be converted, by the prolonged action of the catalyst, into colourless substances.

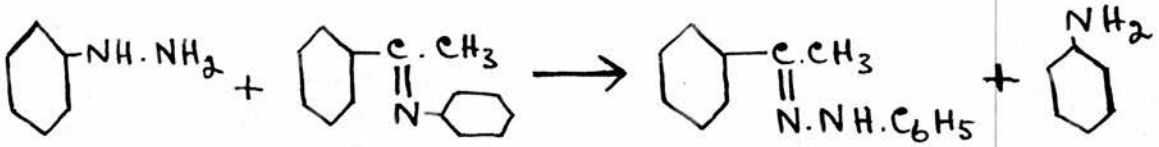
An important difference between the anil and hydrazone fusions is the copious evolution of ammonia in the former. The most probable reason for this is that, in the hydrazone fusion, the ammonia is trapped as soon as formed by the free zinc chloride (or perhaps is only formed as the compound $Zn(NH_3)_4Cl_2$), while in the anil fusion the zinc chloride is bound to the amine arising from the double decomposition, and so is unable to trap the ammonia.

A/

A second difference, fundamentally connected with the first, is the higher temperature required in the anil fusions. This is not due to the double decomposition

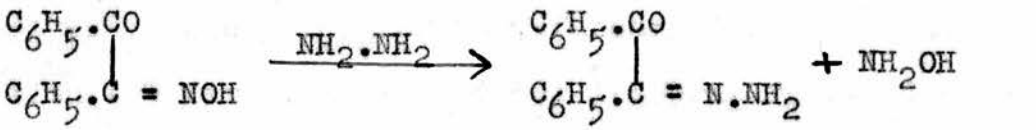
anil + hydrazine ⟶ hydrazone + amine

requiring a higher temperature, since Bodforss has shown that phenylhydrazine and acetophenone-anil give acetophenone-phenylhydrazone and aniline immediately and quantitatively at 60°.

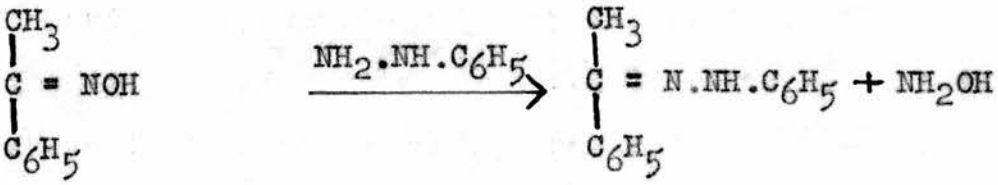


In view of this latter fact, it is evident that an anil fusion represents precisely the same reaction as a Fischer synthesis, except that in it the powerful catalyst, zinc chloride, is replaced by the relatively feeble catalyst, an amine-zincichloride. Herein, therefore, lies the explanation of the higher temperature required by the anil fusion. In confirmation of this we have Reddelien's own observation that the conversion of acetophenone-phenylhydrazone to α-phenyl indole is also brought about by aniline-zincichloride, but only at a much higher temperature (250°).

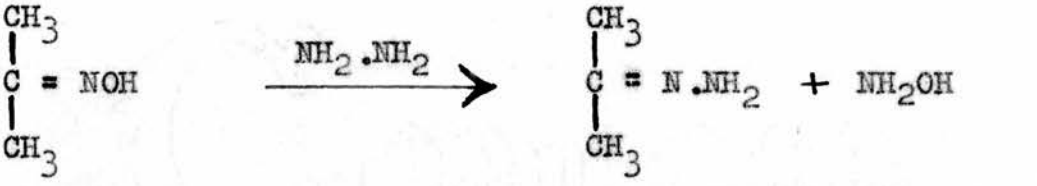
The double decomposition described above is not without parallel in organic chemistry, as witness the following reactions:-



(Forster, J.C.S., 1912, 101, 2234)



(Just, Ber., 1886, 19, 1206)

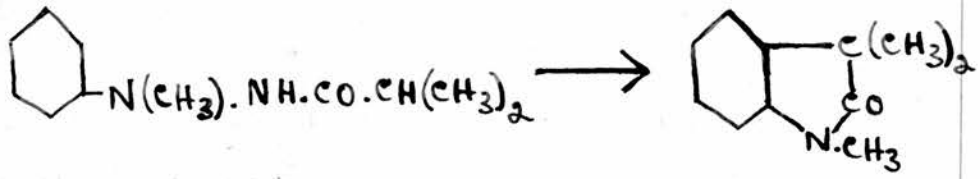


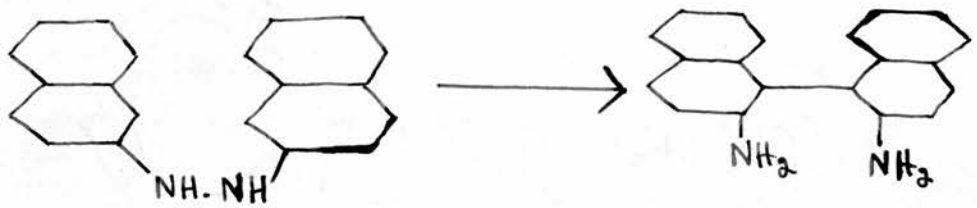
(Rothenburg, Ber., 1893, 26, 2061)

Robinson's mechanism is therefore the only one remaining for serious consideration. Though not yet proved, the correctness of the theory is more than probable, as it gives an adequate explanation of all the observed phenomena, while no valid objection to it has yet been made. It was unfortunate that no definite result was obtained in the attempts made in this thesis to substantiate the theory, as it was felt that the line of attack adopted was a promising one.

Meanwhile some of the views of Robinson call for comment. The latter states that (1) the necessary conditions for a Fischer synthesis are an acid reagent and a high temperature, and that (2) these are precisely the requirements for a benzidine conversion./

conversion. Both of these statements require modification, however, as may be seen by reference to two reactions actually mentioned by Robinson himself, namely, the Fischer synthesis of oxindoles from acid hydrazides, and the ortho-benzidine conversion of β-hydrazonaphthalene to 2:2'-diamino-1:1'-dinaphthyl.

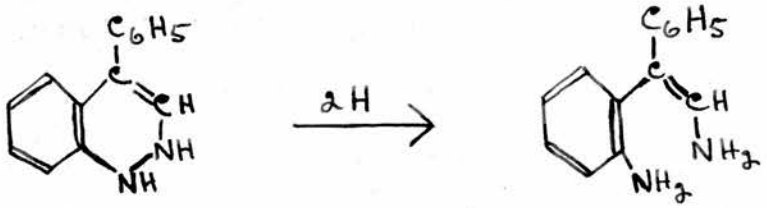




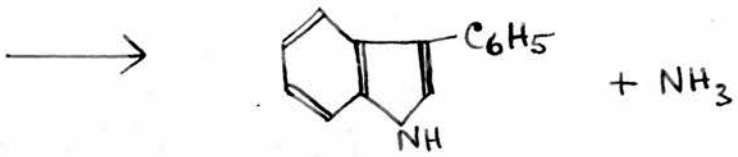
Both of these reactions are brought about by strong alkalis. Finally, the work of Korczynski, Brydowna and Kierzek, (page 9) shows that the Fischer synthesis is catalysed quite readily by such neutral substances as powdered metals, the yields obtained (60% - 65%) being almost as good as with zinc chloride.

It is interesting to note that the production of indoles by reduction of dihydro-cinnolines, and the failure to obtain these compounds by the action of acids on ~~reduction of~~ tetrahydro-cinnolines, besides disproving Neber's theory (see page 148), also affords indirect support/

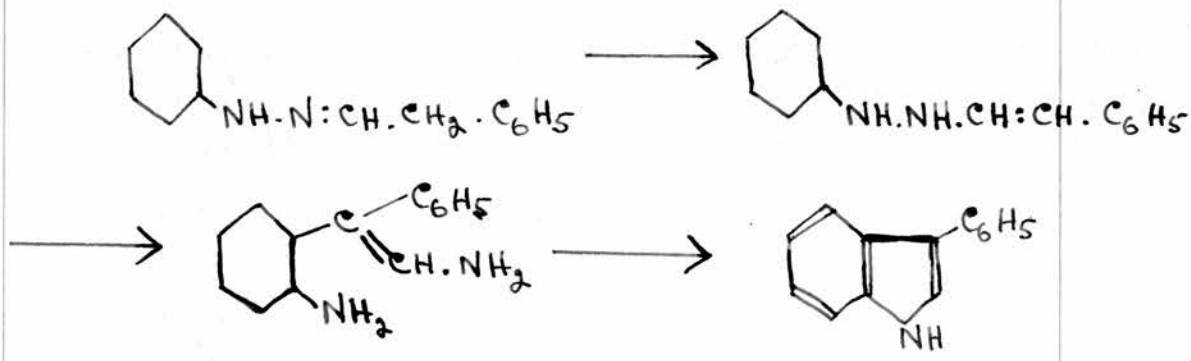
support for Robinson's mechanism, since this result can be readily explained as follows:-



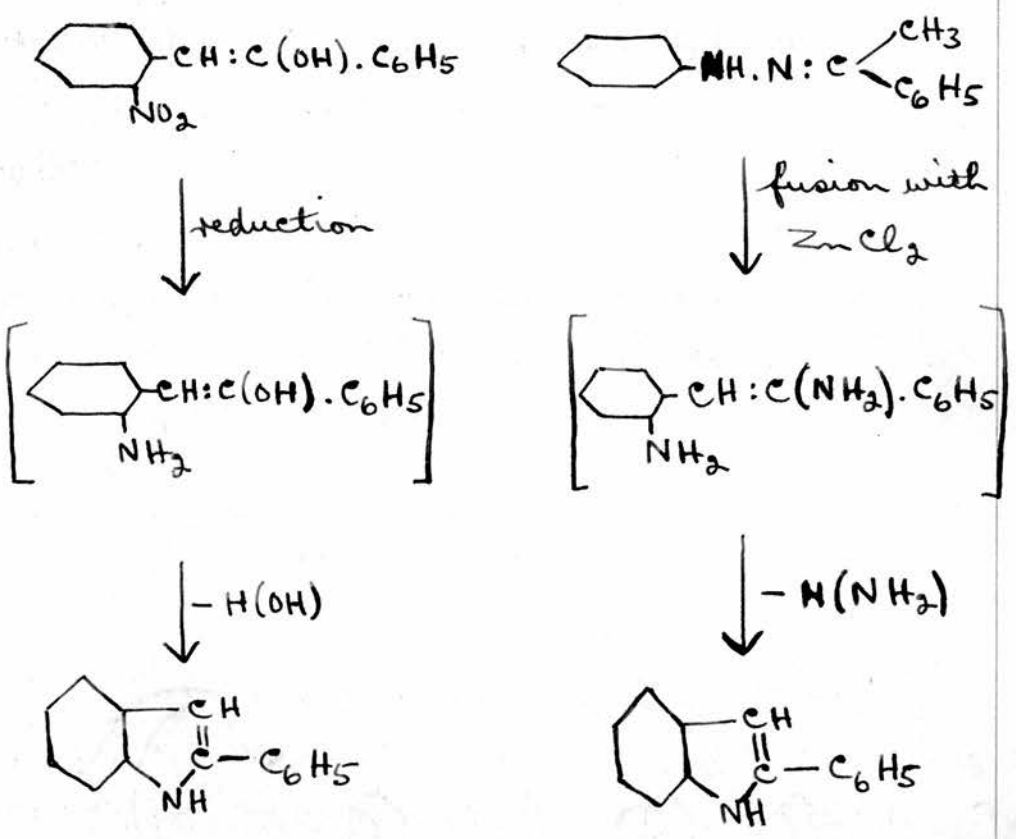
I. II.



This is exactly in accordance with Robinson's theory, as substance II. is precisely the compound postulated by him as an intermediate in the preparation of 3-phenyl-indole from phenylacetaldehyde-phenyl-:hydrazone.



Another point which has so far been overlooked is that the intermediate compound postulated by Robinson in the preparation of α-phenyl indole from acetophenone-phenylhydrazone is of the same form as that assumed in Pictet's synthesis of the compound from ortho-nitro-desoxybenzoïn. This is readily seen from the following comparison:-



In neither case is the intermediate compound shown in brackets isolated, and presumably each undergoes ring closure immediately it is formed.

PART III.

Structure of the Indole "Nitroso-compounds".

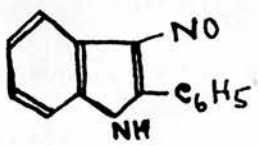
Introduction.

All indole derivatives appear to react readily with nitrous acid, usually with production of definite "nitroso-compounds", in which a hydrogen atom of the indole is replaced by a nitrogen atom and an oxygen atom.

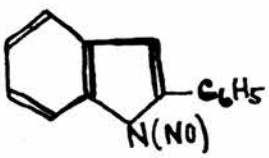
$$R.H + HO.NO \longrightarrow R.NO + H_2O$$

The substances obtained, however, belong to several different types according to the position of the substituents (if any) in the parent compound.

The most important of these "nitroso-compounds" is that of α-phenyl indole, which was first prepared by Möhlau (Ber., 1882, 15, 2480) and assigned the structure 2-phenyl-3-nitroso indole (I.) by Fischer and Schmitt (Ber., 1888, 21, 1073).



I.

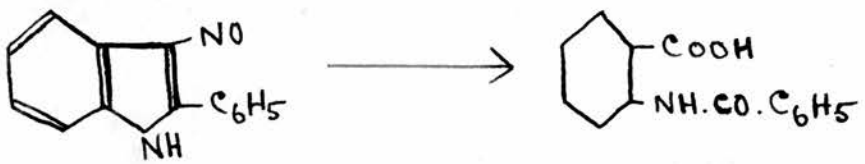


II.

The more obvious N-nitrosamine structure (II.) was inadmissible since the compound did not give the Liebermann reaction and exhibited chemical and physical properties characteristically different from those of known N-nitroso indoles. For example, the/

the "nitroso-compounds" of 3-substituted and of 2:3-disubstituted indoles, which must possess the N-nitroso structure, give the Liebermann reaction, yield the original indoles on reduction, have low melting-points and are readily soluble in the common organic solvent; while "nitroso-α-phenyl-indole" does not give the Liebermann reaction, is reduced to amino-α-phenyl-indole, melts with decomposition at a high temperature and is characteristically insoluble in the common organic solvents.

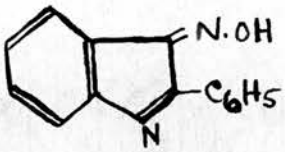
The position of the "nitroso"-group was not definitely proved, however, until 1900, when Angeli and Angelico (Gazz., 1900, 30 (2), 268) oxidised the compound, by the use of several different reagents, to benzoyl-anthranilic acid, thus showing that the "nitroso"-group was neither in the 1- position nor in the benzene ring, and must therefore occupy the 3- position.



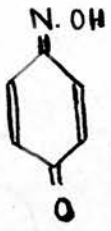
At the same time these authors objected to the nitroso structure, since the compound possessed none of the characteristic properties of the known C- nitroso compounds. The latter are all volatile substances with low melting-points, possessing an intense blue or green colour in the liquid state or in solution, while "nitroso-α-phenyl-indole" melts with/

with decomposition above 250°, is involatile, orange-yellow in colour, and gives yellow or orange solutions in those few solvents in which it is soluble to any appreciable extent.

Angeli and Angelico therefore revived Möhlau's suggestion (Ber., 1885, 18, 166) that the substance was an isonitroso-compound (III.), and drew an analogy between it and p-nitroso-phenol (quinone monoxime) (IV.).

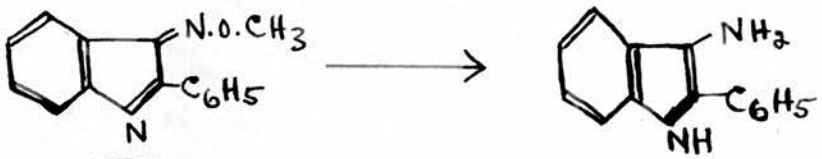


III.



IV.

In support of this hypothesis was quoted the solubility of the compound in alkali, and Möhlau's preparation of the sodium salt (Ber., 1885, 18, 166). Acetyl and benzoyl derivatives and an ethyl ether were also prepared, and the latter substance (V.) shown to give on reduction 2-phenyl-3-amino indole (VI.).

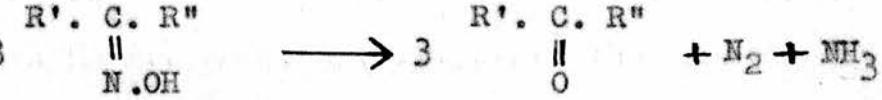


V. VI.

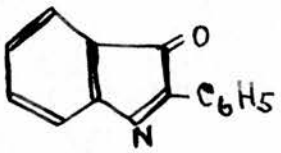
Finally, reference must be made to the important work of Alessandri (Atti R.A.L., (5) 22, II., 150 and 227; Centralblatt 1913, (2), 1486 and 1487), who "confirmed" the oxime structure of "nitroso"-α-phenyl indole as follows:-

It has been shown as a characteristic of ketoximes/

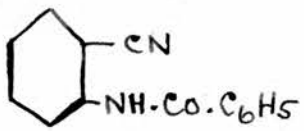
ketoximes that they decompose on heating to give the parent ketone, nitrogen and ammonia, (Angeli and Alessandri, Atti R.A.L.(5), 22, I. 735; Centralblatt 1913, (2), 964).



When "nitroso"-α-phenyl indole is heated above its melting-point, however, the corresponding ketone, α-phenyl indolone VII., is not obtained, but a small quantity of benzoyl-anthranilo-nitrile (VIII.) can be isolated.

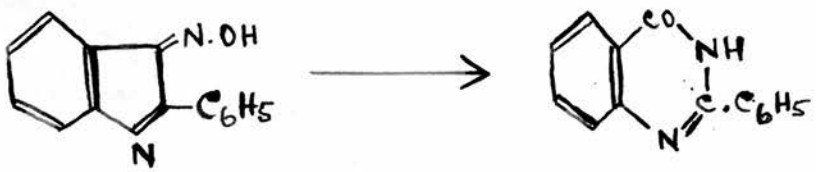


VII.



VIII.

On the other hand, if "nitroso"-α-phenyl indole is treated, in ether suspension, with phosphorus pentachloride at room temperature, the substance obtained is 4-oxy-2-phenyl-dihydroquinazoline (1, 3 benzodiazine), which is precisely what would be the expected product of a Beckmann rearrangement of 2-phenyl-3-isonitroso-indole.



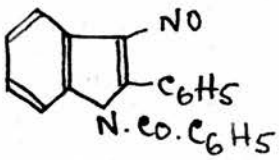
Scope of the Present Work.

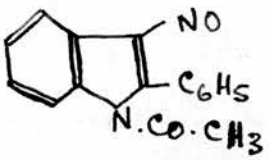
Critical examination of the views of the Italian School:-

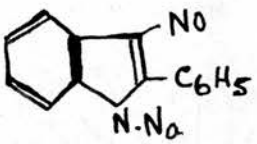
Despite the excellent work of Angeli, Angelico and their co-workers, the conclusions reached by them are not beyond criticism. While carefully pointing out the fundamental differences in properties of the "nitroso"- groups in (a) "nitroso"-α-phenyl indole and (b) nitrosobenzene, these authors fail to show that the former compound shows any of the properties of oximes, except one reaction which might be interpreted as a Beckmann transformation. The oximes are all colourless, crystalline substances, readily soluble in the common organic solvents and melting sharply without decomposition at a moderate temperature. In contrast to this, "nitroso-α-phenyl-indole" is an orange-yellow micro-crystalline compound, characteristically insoluble in almost all solvents and melting with decomposition at a high temperature.

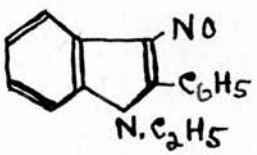
The benzoyl and acetyl derivatives, the sodium salt and the ethyl ether of the latter substance may be formulated as in Column I. instead of according to Angeli and Angelico's scheme in Column II.

Column I.

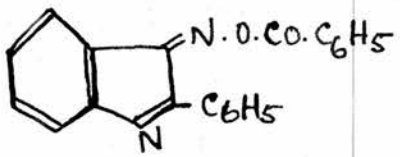


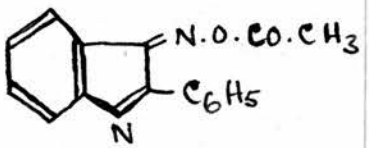


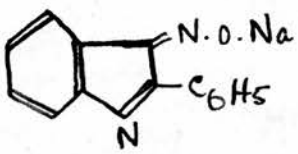


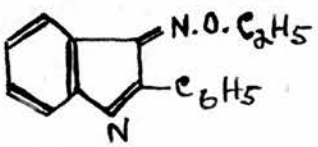


Column II.



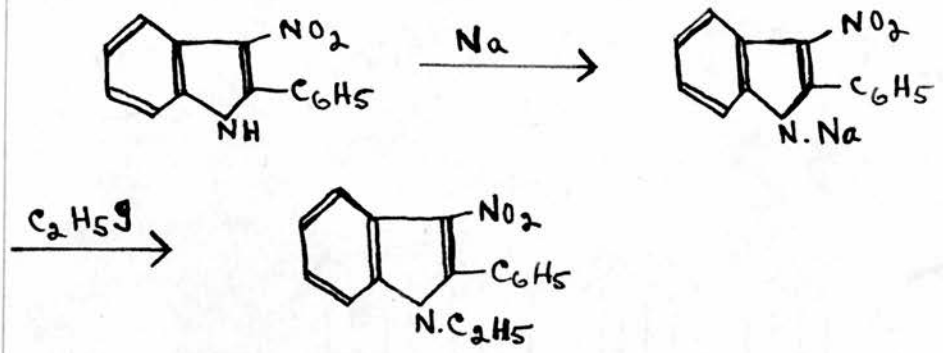






Benzoylation and acetylation of the parent indoles give N-benzoyl and N-acetyl derivatives as well as C-benzoyl and C-acetyl compounds (Zatti and Ferratini, Ber., 1890, 23, 1359; Ciamician and Zatti, Ber., 1889, 22, 1976; Fischer, Ber., 1886, 19, 2988), so that no objection can be raised to the formulation, as in Column I., of the benzoyl and acetyl derivatives of the "nitroso"-compounds. No N-substituted metallic salts of indole derivatives have so far been prepared, but the possibility of their formation cannot be denied, since pyrrole readily forms an N-potassium salt. It is conceivable that the weakening of the phenolic properties of the -NH- group in the pyrrole ring, caused/

caused by its condensation with a benzene ring to form an indole nucleus, is counterbalanced by the introduction of an activating "nitroso"- group in the 3- position. Indeed, the sodium salt and ethyl ether of 3-nitro-2-phenyl indole (obtained by oxidation of 3-"nitroso"-2-phenyl indole), are formulated as the N- derivatives by Angeli and Angelico (Gazz., 1900, 30 (2), 268.)



Finally the structure given in Column I. above to the ethyl ether of "nitroso"-α-phenyl indole has never been disproved, as no "nitroso-compound" of any 1:2 disubstituted indole has so far been prepared. According to Emil Fischer (Ann., 1886, 236, 116) such indoles yield complex dark-brown products with nitrous acid.

Thus if we compare "nitroso"-α-phenyl indole with the true C-nitroso-compounds on the one hand, and with the known oximes on the other, it is seen that no conclusive evidence has been brought forward to place the compound in one category or the other. If an oxime, its strong orange-yellow colour, characteristic insolubility and high melting-point are/

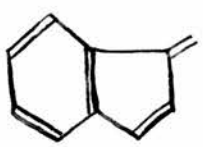
are exceptional; if a true C-nitroso compound, these same three properties are no less so.

Two significant points may be noted; firstly, no true green or blue C-nitroso indole has yet been prepared, and secondly, while "nitroso"-α-phenyl indole is orange-yellow in colour, its benzoyl and acetyl derivatives, its sodium salt and its ethyl ether are of a deep red hue. This latter observation at once suggests the possibility that the orange-yellow compound may be a desmotropic mixture of the C-nitroso-form (blue or green) and the C-isonitroso- form (red).

green or blue true nitroso form.

red isonitroso form.

If the structures attributed by Angeli and Angelico to the benzoyl and acetyl derivatives, the sodium salt and the ethyl ether are accepted, and these substances are formulated as derivatives of the isonitroso form above, it seems at least reasonable to assume that since these four derivatives all possess the same deep red colour, the latter is characteristic of the structure.



It/

It would therefore be expected that 2-phenyl-3-isonitroso indole would also show this colour. (The parent indole, 2-phenyl indole, is white, so that the colour of the "nitroso-compound" and its derivatives is entirely due to the "nitroso"-group or to the alteration of bonds produced by its introduction.) Now "nitroso"-α-phenyl indole has always been described in the literature as a yellow compound melting with decomposition at 258° (except for a few of the earlier workers, who have reported somewhat lower melting-points, 244°, 247° and 250°). It has been found in this research, however, that this melting-point rises steadily on repeated recrystallisation from amyl acetate, until the constant value of 280° is attained, a process accompanied by a steady deepening in the colour of the compound to a distinctly orange shade (see page 99).

It seems not impossible that this deepening in colour and simultaneous rise in the melting-point may represent a shifting of an equilibrium between the nitroso and isonitroso forms in favour of the latter.

The line of experimental attack adopted in this research was as follows:-

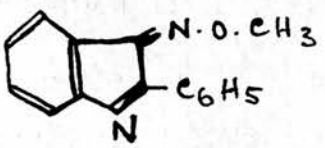
Firstly, the typical reactions of nitroso-benzene/

nitroso-benzene were tried on "nitroso"-α-phenyl indole.

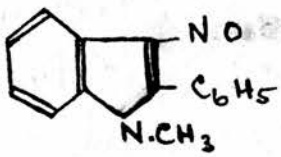
Secondly, because of the marked resemblance in properties between nitrous acid and triphenylcarbinol, the action of the latter substance on α-phenyl indole was investigated.

Thirdly, the ketone corresponding to the oxime form of "nitroso"-α-phenyl indole was prepared, and treated with hydroxylamine.

Fourthly, the methyl ether of "nitroso"-α-phenyl indole (I.) and the nitroso-compound of 1-methyl-2-phenyl indole (II.) were prepared and shown to be different.



I.



II.

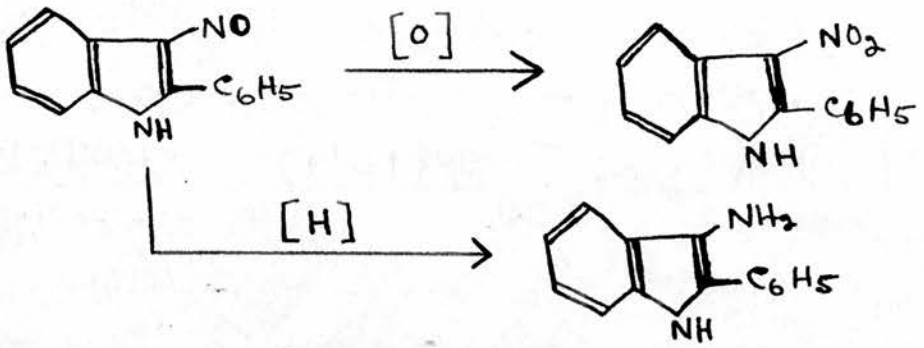
The absorption spectra of these two compounds and that of "nitroso"-α-phenyl indole were determined and compared.

In this way the structure of the methyl ether and of the parent "nitroso-compound" were definitely proved for the first time.

EXPERIMENTAL.

I. Comparison of "nitroso"-α-phenyl indole with nitrosobenzene.

(1) Nitrosobenzene is reduced to aniline and oxidised to nitrobenzene. In the same way "nitroso"-α-phenyl indole is reduced to amino-α-phenyl indole and oxidised to nitro-α-phenyl indole:-



(2) Nitrosobenzene reacts readily with hydrazobenzene to give phenylhydroxylamine and azobenzene:-

$$C_6H_5.NO + C_6H_5.NH.NH.C_6H_5 \longrightarrow$$
$$C_6H_5.NHOH + C_6H_5.N{:}N.C_6H_5.$$

Hydrazobenzene and "nitroso"-α-phenyl indole were dissolved together in a little pyridine and the solution boiled for some time. Alcohol was then added, then water, when a golden yellow precipitate was formed. This was filtered off, when a colourless filtrate was obtained. The residue was washed with a little alcohol, but the washings showed no trace of the red colour of azobenzene.

(3) Nitrosobenzene reacts readily with aniline to give azobenzene:-

$$C_6H_5.NO + C_6H_5.NH_2 \longrightarrow C_6H_5.N{:}N.C_6H_5 + H_2O$$

"Nitroso"-α-phenyl indole was boiled in aniline solution for 2 hours under reflux without showing a trace of condensation with the solvent.

(4) Nitrosobenzene reacts at once with hydroxylamine hydrochloride to give benzenediazonium chloride:-

$$C_6H_5.NO + H_2N.OH, HCl \longrightarrow C_6H_5.N_2Cl + 2H_2O$$

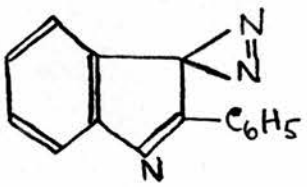
"Nitroso"-α-phenyl indole does not react with hydroxylamine hydrochloride, as was shown as follows:-

A solution of the latter substance in excess sodium carbonate solution was added to a caustic soda solution of α-naphthol and "nitroso"-α-phenyl indole, but no reaction took place either in the cold or on boiling. If nitrosobenzene is substituted for "nitroso"-α-phenyl indole in the above experiment, a red azo dye, phenylazo-α-naphthol is obtained immediately in the cold, owing to the coupling of the α-naphthol with the benzenediazonium chloride formed (Bamberger, Ber., 1895, 28, 1218).

It is evident, therefore, that except for its behaviour on oxidation and reduction, "nitroso"-α-phenyl indole shows none of the typical reactions of nitrosobenzene. At first sight this would appear to constitute conclusive evidence against the nitroso structure/

structure for the former compound, since even the behaviour of the substance on oxidation and reduction can be readily accounted for on the alternative isonitroso formulation.

Indeed Angeli ("Neue Studien in der Indole- und Pyrrolgruppe", 1911) states that the failure of "nitroso"-α-phenyl indole to react with hydroxylamine, the only reaction he used to compare the substance with nitrosobenzene, is conclusive evidence against the nitroso structure. Actually, however, the failure of the latter reaction is not surprising, since the diazo-compounds of the indoles do not resemble at all those of the benzene series, being very stable, intensely orange-yellow coloured substances possessing the structure III below (Castellana and d'Angelo, Gazz., 1906, 36, 56).



III.

It is not likely therefore, that such a compound would be formed by the action of hydroxyl-:amine on 2-phenyl-3-nitroso indole, in the same way as benzenediazonium chloride is formed by the action of hydroxylamine on nitrosobenzene. Even if it were formed, it is not likely that it would couple with α-naphthol to give an azo dye.

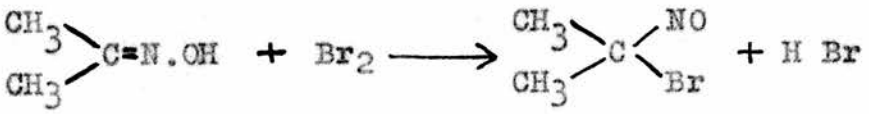
In fact, the strong resemblance between the indole diazo compounds and the aliphatic ones, and the/

the sharp distinction of both from the corresponding substances in the aromatic series, lead one to infer that the indole "nitroso"-compounds should be compared with the aliphatic nitroso-compounds and not with the aromatic members of the group. Unfortunately, however, the chemical reactions of nitroso-butane and the other aliphatic nitroso-compounds do not appear to have been studied much, with the result that this comparison is impossible to make in the absence of definite knowledge, regarding the chemical properties of the latter. Further experimental evidence on this point is given on page 206.

Finally, if "nitroso"-α-phenyl indole were a true ketoxime it might be expected to give Piloty's test:-

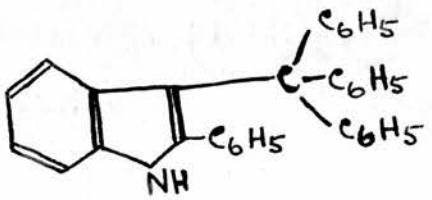
A dilute solution of the "nitroso"-compound in pyridine was treated with a dilute solution of bromine in the same solvent. No reaction took place, however, and the "nitroso"-compound was recovered unchanged on pouring the mixture into water.

This reaction is a very delicate test for aliphatic ketoximes, a deep blue colouration being produced immediately on addition of bromine, due to formation of bromo-nitroso compounds.

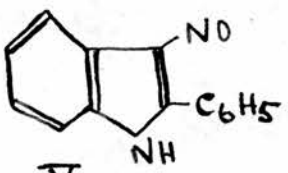


II. Condensation of α-phenyl indole with triphenylcarbinol.

The remarkable similarity in chemical relations shown by nitrous acid and triphenylcarbinol is well known (see Sidgwick's "Chemistry of Nitrogen", page 8, for a summary of the points of resemblance). It was therefore of interest to see if triphenylcarbinol would condense with α-phenyl indole in the same way as nitrous acid. If such a condensation product were obtained (IV.) it would correspond to the true nitroso structure of nitroso-α-phenyl indole (V.).



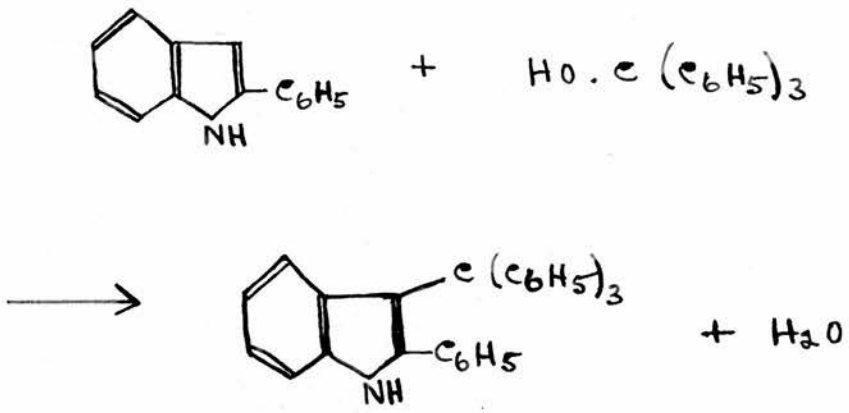
IV.



V.

α-Phenyl indole (0·4 gm.) and triphenylcarbinol (0·9 gm.) were dissolved separately in boiling glacial acetic acid, and the two solutions mixed. A purple colouration was produced immediately, but no precipitate appeared. Water was then added, when a reddish-grey substance was thrown down. This was filtered off and recrystallised from alcohol, from which it separated as colourless truncated prisms melting sharply at 212°.

The yield obtained was 0·32 gm., representing 36% of the theoretical.



Nitrogen analysis:- (Micro-Dumas method)

Found	N 3·20%
Calculated	N 3·22%

The alcoholic solution of the substance shows a much stronger purple fluorescence than the parent indole. It also gives Ehrlich's test (page 91), but not the pine-splint reaction - the latter failure being a general, though not universal, characteristic of 2:3-disubstituted indoles.

The above substance was previously unknown, but Pieroni and Veremeenco (Gazz., 1926, 56, 468) have obtained a similar compound (melting at 180°) from α-methyl indole.

III. Determination of the Molecular Weight of "Nitroso"-2-phenyl-6-methyl indole.

This was carried out in order to determine whether the abnormally high melting-points of the "nitroso"- compounds of α-phenyl indole and its Bz-methyl homologues could be attributed to association/

association of the substances to form double molecules, in the same way as Zatti and Ferratini (Gazz., 1891, (21) 2, 19) have attributed the abnormally high melting-point (174°) of N-nitroso indole to this cause.

Rast's method:-

0·0086 gm. of 3-"nitroso"-2-phenyl-6-methyl indole and 0·1493 gm. of camphor were weighed out in a sublimation tube, the neck of which was then sealed. The mixture was fused to a homogeneous melt (clear solution of the "nitroso"-compound in camphor), which was then allowed to cool. The tube was broken and the "melting-point" of the contents determined in the usual way and compared with that of the sample of pure camphor used.

The "melting-point" taken was that at which the last crystals disappeared, and was found to be 9·0° below that of the sample of pure solvent.

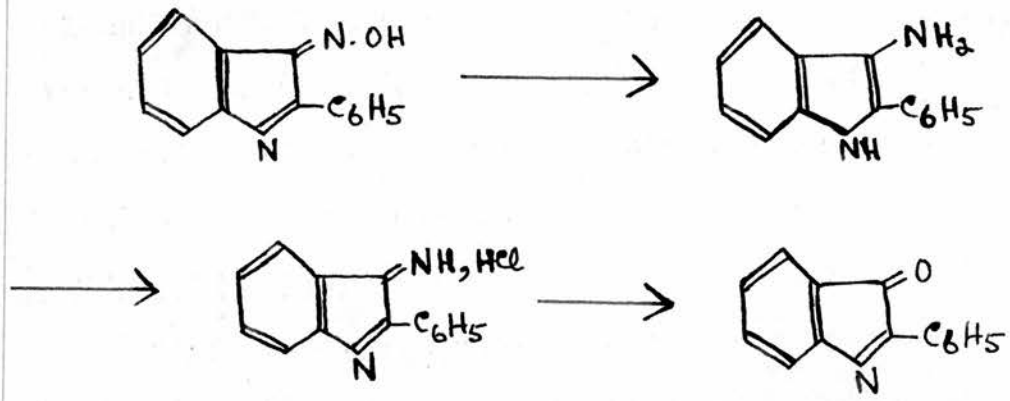
Hence Molecular Weight $= \frac{40,000 \times 0·0086}{9·0 \times 0·1493} = \underline{231}$.

The single formula, $C_{15}H_{12}N_2O$, requires 236.

It is thus evident that the abnormally high melting-points of the "nitroso"- compounds of the type under consideration cannot be attributed to molecular association.

IV. Preparation of 2-phenyl-indolone.

Kalb and Baeyer, Ber., 1912, 45 (2), 2150.



(1) Preparation of 3-amino-2-phenyl indole.

"Nitroso"-α-phenyl indole (7 gm.) was dissolved by heating in a mixture of 40 c.c. of 2 N. sodium hydroxide and 20 c.c. of alcohol. Sodium hydrosulphite ($Na_2S_2O_4$, 15 gm.) was now added gradually with shaking. The mixture was cooled rapidly and filtered, the residue washed with water and alcohol, and dried rapidly.

The yield obtained was almost theoretical (6·5 gm.).

(2) Preparation of 3-imino-2-phenyl indole.

The finely powdered 3-amino-2-phenyl indole (6·5 gm.) was suspended in 100 c.c. of benzene, and 25 gm. of lead peroxide added. The mixture was heated on a water-bath, with frequent shaking, until a test portion showed no green colour on filtering and warming the filtrate with acetic acid.

The mixture was then filtered and the residue washed with hot benzene. The deep yellow filtrate

was/

was evaporated under reduced pressure until crystallisation commenced, when the imino-compound was obtained in gleaming orange-yellow leaflets.

The yield obtained was 4·5 gm., representing 69% of the theoretical.

(3) Preparation of 2-phenyl-3-indolone.

The imino- compound obtained above (4·5 gm.) was ground up in a porcelain basin with just sufficient concentrated hydrochloric acid to convert the whole of the orange-yellow compound into a deep brown mush (a few drops of acid were sufficient). This was immediately pressed on a porous saucer until powdery, and then dried more completely in a vacuum desiccator over soda-lime. The finely powdered substance (4·5 gm.) was boiled with 230 c.c. of benzene, and 1 gm. of finely powdered chalk added to complete the removal of hydrochloric acid. After evaporation of the benzene solution to small volume (in vacuo), it was treated with twice its volume of petrol ether. A yellow precipitate of the ketone hydrate separated and was filtered off. The filtrate was evaporated to small bulk and allowed to crystallise, when 2-phenyl indolone separated as bright scarlet crystals melting at 100°-102°. The yield obtained was 4 gm., representing 90% of the theoretical.

The overall yield of 2-phenyl indolone from "nitroso"-α-phenyl indole was therefore 60%.

V. Action of hydroxylamine on 2-phenyl-indolone.

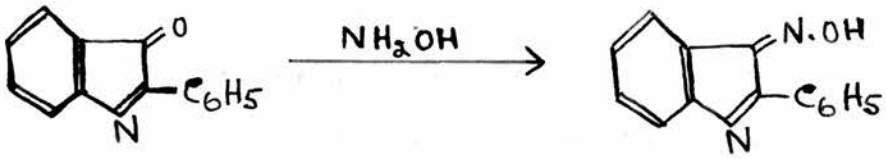
Hydroxylamine hydrochloride and 2-phenyl indolone were dissolved separately in alcohol, and the solutions mixed. A green colouration was produced at once, which, on boiling the mixture, became very dark green, then brown, then deep red. No further change took place, even after boiling for one hour, but on addition of powdered sodium acetate trihydrate the formation of a yellow precipitate commenced at once.

After boiling for one hour longer, the yellow precipitate was filtered off, washed successively with alcohol, water, alcohol and ether, and then recrystallised from amyl acetate. An orange-yellow substance was obtained melting at 280° with decomposition and showing no melting-point depression when mixed with "nitroso"-α-phenyl indole (m.p. 280° (d.)).

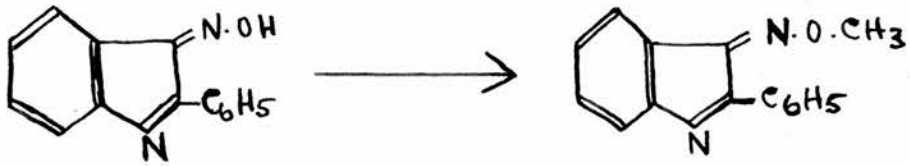
In order to establish with absolute certainty the identity of the substance obtained with "nitroso"-α-phenyl indole, the former was benzoylated by the procedure described on page 107, and the resultant product shown by melting-point and mixed melting-point (153°) to be the benzoyl derivative of "nitroso"-α-phenyl indole (m.p. 153°).

It is evident, therefore, that "nitroso"-α-phenyl indole is identical with the oxime of 2-phenyl-indolone, or at least tautomeric with it, and/

and that until definite evidence is produced in favour of the true nitroso structure, the substance must be formulated as the isonitroso compound, thus:-



VI. Preparation of 2-phenyl-3-methyloximo-indole.



0·46 gm. sodium

25 c.c. dry methyl alcohol

2·84 gm. methyl iodide

4·44 gm. 2-phenyl-3-isonitroso indole.

The sodium was dissolved in the methyl alcohol and the isonitroso-compound added. The latter dissolved immediately with formation of a deep red solution of the sodium salt. The methyl iodide was then added, and the mixture boiled under reflux for one hour. On evaporating off the alcohol and washing the residue with dilute sodium hydroxide solution, a dark red substance was obtained. This was taken up in benzene, the benzene solution washed with dilute caustic soda then water, dried over sodium hydroxide, and evaporated to dryness.

A viscid dark-red syrup was obtained (3·3 gm.) which would not recrystallise from ligroïn, alcohol, ether/

ether, benzene, acetone or chloroform. With each of these solvents the substance seemed miscible in all proportions. On extracting the compound with petrol ether (b.p. 40°-60°) in a Soxhlet apparatus, a clear ruby red solution was obtained and a small amount of black insoluble material left behind.

The petrol ether solution was evaporated to dryness on the steam-bath, and the viscid dark-red syrup remaining freed from the last traces of solvent in a vacuum desiccator evacuated to a pressure of 0·5 m.m.. After a week the substance began to solidify to a bright red crystalline mass, a process which was only complete after several weeks' standing under a pressure of 0·5 m.m..

The substance melted sharply at 54°, softening slightly at 52·5°. A small sample was distilled in vacuo using the very simple but efficient micro-vacuum-distillation apparatus of Pregl, when 0·2 gm. of pure substance was obtained boiling at 193°-195° at 0·4 m.m. pressure. Almost the whole of the material used distilled over a range of two degrees and very little loss was sustained.

Nitrogen analysis:- (Micro-Dumas method)

Found	N	11·8%
Calculated	N	11·9%

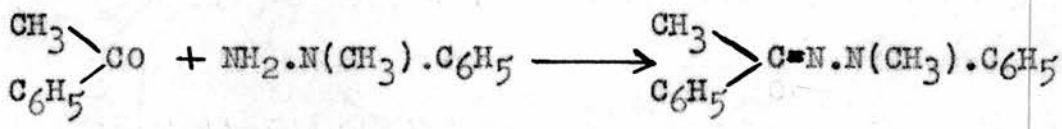
2-Phenyl-3-methyloximo-indolone was thus obtained as a bright red crystalline substance melting/

melting at 54°, boiling at 193°-195° under 0·4 m.m. pressure, and too soluble in alcohol, ether, benzene, ligroïn, light petroleum, carbon disulphide, acetone or chloroform to be recrystallisable from those media.

VII. Preparation of 1-methyl-2-phenyl-3-nitroso-indole.

(1) Preparation of acetophenone-methylphenyl-hydrazone.

Degen, Ann., 1886, 236, 154.



25 gms. acetophenone

25 gms. methylphenylhydrazine

The two reactants were heated together on the steam-bath for several days without result, a circumstance which is discussed more fully on page 34 . The mixture was therefore fractionally distilled in vacuo, two fractions being collected. The first, distilling from 80° to 140° at 12 m.m. pressure, consisted of unchanged reactants, and amounted to 7 gm. or 14% of the original material. The second fraction, boiling at 186°-192° at 11 m.m. pressure, consisted of the hydrazone, and was obtained as a thick, viscid, pale yellow syrup which crystallised with extreme slowness (cf. acetophenone-m-tolylhydrazone, page 38).

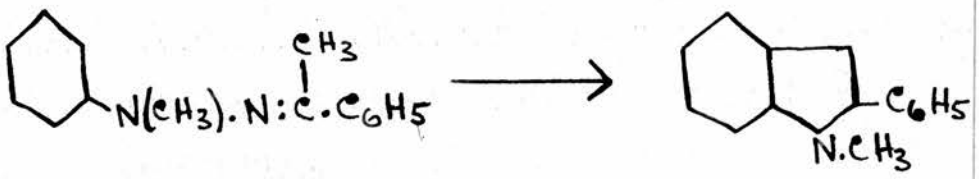
The yield obtained was 24 gm., representing

52%/

52% of the theoretical. By recrystallisation of the syrup from ligroïn the substance was obtained as crystals melting at 49°-50°.

(2) Prepration of 1-methyl-2-phenyl indole.

Degen, Ann., 1886, 236, 154.



Acetophenone-methylphenylhydrazone (24 gm.) was mixed with powdered anhydrous zinc chloride (120 gm.), and the mixture heated in a nickel crucible for 5 hours at 130°. The resultant mixture was boiled with very dilute hydrochloric acid to extract zinc chloride, filtered, and the residue distilled in vacuo. The indole distilled at 214° under 32 m.m. pressure, giving a yield of 9 gm. or 40% of the theoretical. This distillate was a clean, almost white product, melting at 95°-96°, and was not purified further as this led to considerable loss and the indole was only required for conversion into the nitroso-compound. Degen quotes m.p. 100°-101°.

(3) Improved method of preparing 1-methyl-2-phenyl indole.

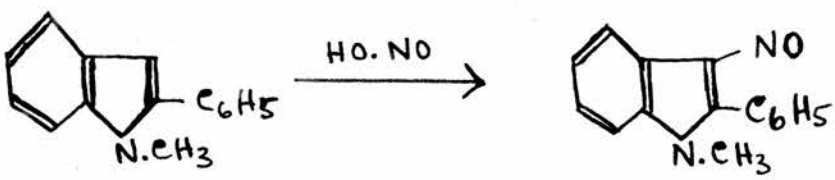
As a result of the numerous abortive attempts to obtain α-phenyl-m-toluindole by the use of low fusion/

fusion temperatures, and the ultimate successful preparation of this substance in excellent yield at an unusually high temperature, it was considered that short exposure to a high temperature was more effective than more prolonged exposure to a lower temperature in effecting the conversion of hydrazones into indoles, and that therefore a greater yield of 1-methyl-2-phenyl indole would be obtained by replacing the 5 hours fusion at 130° by a shorter fusion at a higher temperature.

This prediction was borne out by experiment, when it was found that 8 gms. of acetophenone-methylphenylhydrazone, when fused with 40 gms. of zinc chloride at 200°, underwent indole formation within two minutes giving a yield of 4 gms. of indole representing 54% of the theoretical (5 hours fusion at 130° gave a 40% yield).

(4) Action of nitrous acid on 1-methyl-2-phenyl indole.

Should this substance form a "nitroso"-derivative it is evident that the latter must be a true C-nitroso compound with the -NO group occupying the very reactive 3- position of the parent indole.



On the one hand it is most improbable that the nitroso- group should enter the benzene ring portion of the indole nucleus, and on the other hand the formation of an isonitroso-compound is impossible.

According to Degen (Ann., 1886, 236, 154) 1-methyl-2-phenyl indole gives a "complex dark brown product" with nitrous acid, while according to Emil Fischer (ibid.) 1:2- disubstituted indoles in general do not give any definite products with this reagent.

Preparation of 1-methyl-2-phenyl-3-nitroso-indole.

1-Methyl-2-phenyl indole (1·0 gm.) was dissolved in cold glacial acetic acid and treated with a concentrated aqueous solution of sodium nitrite (about 0·5 gm.). A red solution was formed at once, and this, on pouring into water, gave what appeared to be a pale yellowish-green precipitate. On filtering, and washing the residue with water, however, a clean emerald green product was obtained, which, on recrystallisation from ligroïn, gave beautiful long narrow emerald green plates, melting at 143°-144°. After a second recrystallisation from that solvent, the substance melted sharply at 144·5°.

The yield obtained was 0·97 gm., representing 85% of the theoretical.

The substance was readily obtained by the standard method, and was of such a striking colour that/

that the failures of Fischer and Degen to obtain it are surprising. If the nitroso-compound was prepared from very impure indole, such as that obtained by evaporation of recrystallisation mother-liquors, the primary product obtained was pitch black and resembled a piece of hardened tar. From this, however, the nitroso-compound was readily obtained by extraction with boiling ligroïn.

The compound was insoluble in water, dilute sodium hydroxide solution and cold ligroïn, but soluble in alcohol, ether, benzene, chloroform, carbon disulphide, acetone and boiling ligroïn. Glacial acetic acid appeared to decompose the compound with production of a brownish solution. The substance dissolved in concentrated sulphuric acid with production of a deep red solution. It did not, however, give the Liebermann reaction and did not react with aniline, hydroxylamine or hydrazobenzene. Since, therefore, there can be no dubiety regarding the true nitroso structure of the compound now under examination, it follows that the evidence advanced on pages 190 to 192 against this structure being assigned to "nitroso"-α-phenyl indole becomes at once invalid, as it has now been shown that the nitroso group (-NO) in the 3- position of the indole ring does not give the typical reactions of the same group in nitrosobenzene.

It is evident, therefore, that no valid evidence/

evidence remains to conflict with the view that "nitroso"-α-phenyl indole is a true nitroso- compound tautomeric with the oxime of 2-phenyl-indolone (page 199), a theory strongly supported by the colour relations of the compound (see below).

Determination of the Absorption Spectra of (a) "Nitroso"-α-phenyl-Indole, (b) the Methyl Ether of "Nitroso"-α-phenyl-Indole and (c) 1-Methyl-2-phenyl-3-nitroso-Indole.

This was undertaken in order to test the above hypothesis that "nitroso"-α-phenyl indole is a tautomeric mixture of the isonitroso and true nitroso forms. This employment of physical methods appeared to be necessary, as it did not seem possible, in the light of present knowledge, to attack the problem directly by chemical means, since no characteristic reactions of true indole nitroso-compounds are known by which the presence of the nitroso form could be detected.

Since, however, only the latter form contains the -NH- group, it would seem that the most direct method of approach would be to determine whether or not the absorption spectrum of the substance showed the band at 2·9 - 3 μ characteristic of this group. Unfortunately, this was so far into the infra-red as to be beyond the reach of any apparatus available.

The/

The method therefore adopted was to determine and compare the absorption, in the visible and ultra-violet regions, of the three substances mentioned in the heading, in order to ascertain whether the absorption spectrum of "nitroso"-α-phenyl indole resembled that of its methyl ether or that of a true indole nitroso-compound, 1-methyl-2-phenyl-3-nitroso-indole.

(a) Experiments in the Visible Region.

Since the methyl ether and the true nitroso-indole are both strongly coloured and are respectively red and green, it follows that these two substances possess absorption bands at the blue and red ends of the visible spectrum respectively. Moreover, since the parent indoles are themselves colourless, it is evident that these absorption bands are due solely to the groups $=N\cdot OCH_3$ and $-NO$. Should, therefore, "nitroso"-α-phenyl indole possess both of these bands, it will, presumably, be a desmotropic mixture of the true nitroso and isonitroso forms, whereas, should it possess only one of these characteristic bands, it will be a homogenous species possessing the structure corresponding to the particular band found.

The three substances were examined by the Baly tube method in solutions of concentration 0·0004 M. in ordinary absolute alcohol, this being about the highest concentration of the isonitroso-compound obtainable in this solvent. No purification of the latter/

latter was made before use as this was unnecessary. A Bellingham and Stanley glass spectrograph was used, giving the spectrum from 700 mμ - 420 mμ on a 10 inch photographic plate. In the absence of any special source of light, an ordinary 60 watt lamp was utilised for this purpose, being placed about 30 cms. from the slit of the spectrograph. Specially rapid Ilford panchromatic plates were employed, and the solutions were examined in layers of 3 - 95·5 m.m..

The same series of exposures were made through the same series of solution depths, in the case of all three compounds, so that the plates obtained were directly comparable. It was found that the plates obtained with "nitroso"-α-phenyl indole and its methyl ether both showed only one "half" of a single absorption band, the head of which lay beyond the spectral limits of the plate (i.e. below 420 mμ). The two plates were quite indistinguishable except that the absorption edge lay slightly nearer the red end in the case of the methyl ether. No absorption was detected at the red end of the spectrum in either plate. It was already evident, therefore, that "nitroso"-α-phenyl-indole possessed that band at the blue end of the spectrum which may justifiably be attributed to the isonitroso structure.

Unfortunately, the plate for the green nitroso-compound showed no absorption at all, even through a 10 c.m. layer. It was therefore apparent that the absorption bands of this compound would only be observable/

observable with a much more concentrated solution. Such a solution could have been obtained in a different solvent, but this would have been to no purpose, since a correspondingly concentrated solution of "nitroso"-α-phenyl indole would have been required in order to detect the presence of the nitroso band in it. Such a solution (0·1M.) could not be obtained in any neutral solvent tried, including alcohol, ether, benzene, petroleum, acetone, carbon disulphide, ethyl acetate, amyl acetate, chloroform, anisole and acetophenone. Only in such solvents as glacial acetic acid, aniline and pyridine could a sufficiently concentrated solution be prepared, and these could not be used since they dissolved the substance with compound formation, a circumstance which would completely alter the absorption spectrum. Moreover, aniline and pyridine, being bases, would displace any equilibrium between the nitroso form (feebly basic) and the isonitroso form (distinctly acidic) almost completely in favour of the latter.

These experiments in the visible region, therefore, showed that "nitroso"-α-phenyl indole consisted, at least in part, of the isonitroso form, but failed, on account of the insolubility of the compound, to decide whether or not it contained any of the true nitroso species.

(b) Absorption Spectra Measurements in the Ultra-Violet Region.

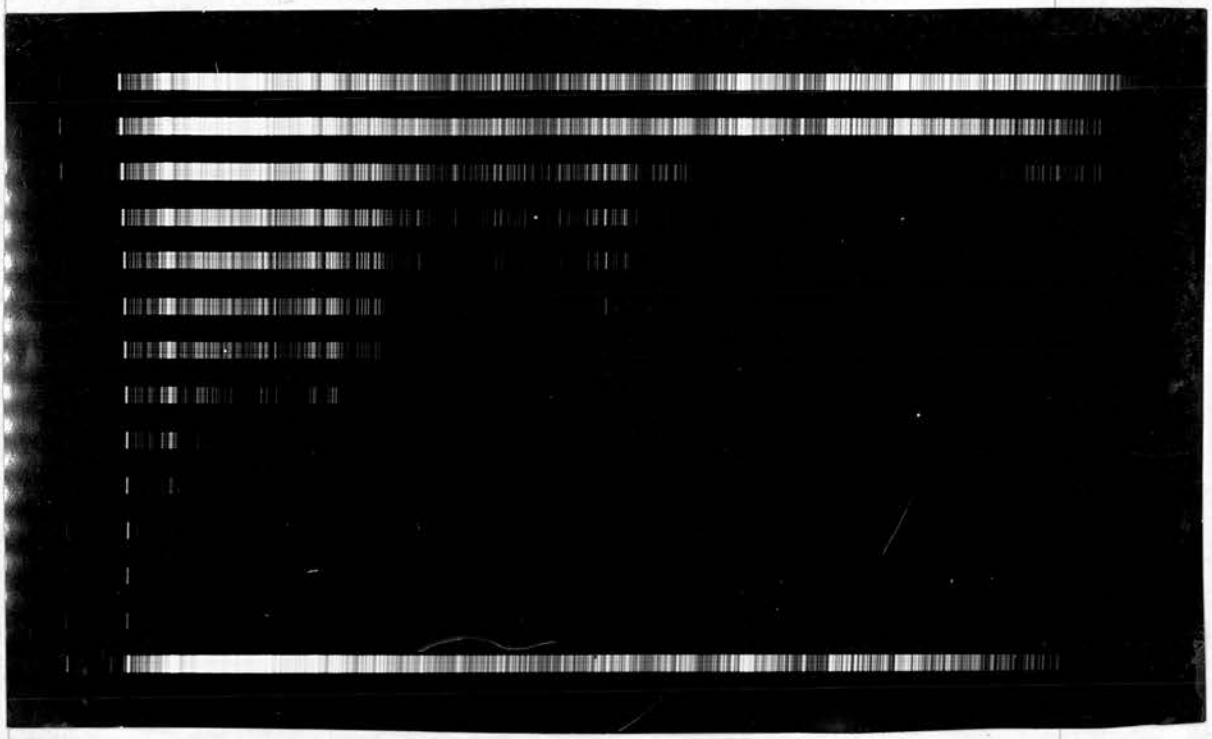
A Bellingham and Stanley "medium" quartz spectrograph was used, giving the spectrum from about 205 mμ to the red region on a 10x4 inch plate. The solutions used were the same as for the previous work in the visible region, so that measurements could be made down to 230 mμ, the point at which the solvent began to absorb.

The source of light was an iron spark, 2-3 m.m. in length, connected in series with a second smaller spark and placed inparallel with a condenser of about 0·025 microfarad capacity. The spark was worked by a transformer giving about 6,000 volts across the secondary.

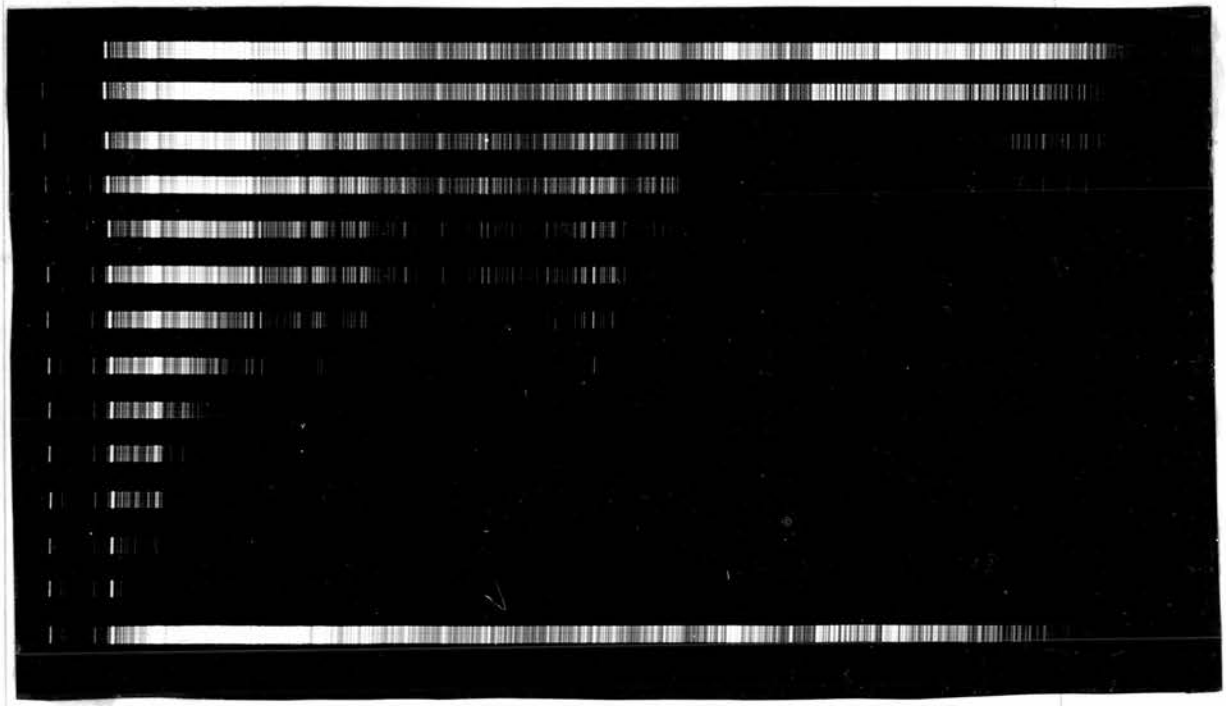
At first the Baly tube method was employed, and consecutive exposures taken on the same plate using the same solution in a series of depths forming a geometrical progression. Since, therefore the exposures were equally spaced on the plate, and the logarithms of a geometrical progression form an arithmetical progression, the plates, when developed, gave a qualitative picture of the absorption curve obtained by plotting the wavelengths of the edges of the absorption against the logarithms of the depths of solution. This was the old method of representing absorption curves.

Positives of the photographs thus obtained for the three substances are shown on the opposite page. These/

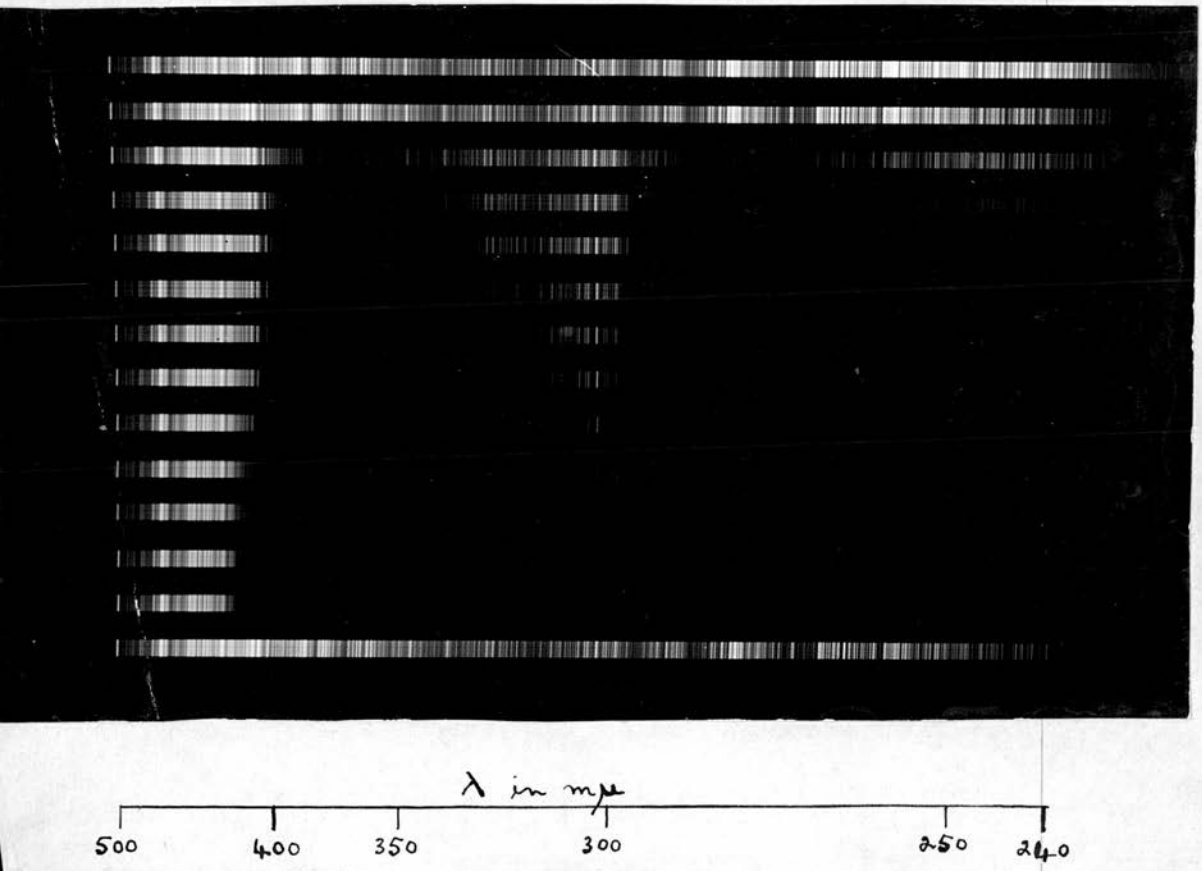
2-Phenyl-3-methyloximo-indolone.



"Nitroso"-α-phenyl Indole.



1-Methyl-2-phenyl-3-nitroso-indole.



These leave no doubt that the absorption spectrum of "nitroso"-α-phenyl indole is very similar to that of its methyl ether and quite different from that of 1-methyl-2-phenyl-3-nitroso indole.

In order that a quantitative determination of the absorption curves might be made, however, it was necessary to use the "rotating sector" method described below:-

The curve to be determined was that showing the variation of log k with the wave-length, where k is the "extinction coefficient" derived from the Beer-Lambert Law,

$$\log \frac{I_o}{I} = k.c.d,$$

in which I_o and I are respectively the incident and emergent intensities of a beam of monochromatic light passing through a depth d of a solution of concentration c. (C and d are usually measured in moles per litre and in cm. respectively, and logs are taken to the base 10).

The solution under examination was contained in cells of different sizes, the largest (2 c.m.) having screw-on ends while the smaller ones (1 m.m. and 4 m.m.) consisted of glass distance pieces with quartz end-plates held in place by spring clips. The exact depths of liquid in each cell was deter-:mined by means of a micrometer screw gauge.

In order to determine the ratio $\frac{I_o}{I}$, a second "comparison spectrum" was provided, in conjunction with/

with a "rotating-sector" photometer, as follows:-

Solvent and solution were contained in two precisely similar cells, mounted side by side so that their axes were inclined at equal (small) angles to that of the collimator of the spectrograph. The iron spark was placed at the intersection of these axes, a latitude of two or three millimetres being allowable. The two beams of light, after passing through the cells, were refracted by a fixed optical arrangement so as to be passed into the slit of the spectrograph one above the other. In this way each exposure of the plate gave a double spectrum, one portion being taken through the solvent and one through the solution.

In front of the cells (i.e. between them and the spark) was placed the "rotating sector" photometer. This consisted of two equal solid wheels driven round rapidly at the same speed by the same electric motor. In each wheel two sectors had been cut out at opposite ends of a diameter, the resultant "sector openings" being fixed in one wheel and of variable aperture in the other. These wheels were so arranged that the light from the spark was completely cut off from the cells except when the sector opening passed in front of them, the light passing through the solution being controlled by the fixed wheel and that through the solvent by the variable wheel.

In each exposure the sector opening of the latter was cut down by different known amounts, so that/

that, at the points of equal blackening of the two portions of the double spectrum on the plate, the ratio $\log \frac{I_o}{I}$ for the solution was given by the log of the ratio of the fixed and variable sector openings. Actually, however, the variable sector was graduated in terms of this ratio, for which values from 0-2·0 were obtainable.

The wave-lengths of the points of equal blackening were picked out by comparison with a large scale chart of the iron spark spectrum, and the values of λ obtained plotted against the corresponding values of log $\underline{k}$ found from the equation previously given,

$$\log \frac{I_o}{I} = k.c.d.$$

The curves thus obtained for the three substances examined are shown on the opposite page and leave no doubt of the identity in structure of "nitroso"-α-phenyl indole and its methyl ether. At the same time the curve of the true nitroso-compound is quite different and none of its characteristics appear in that of the first substance.

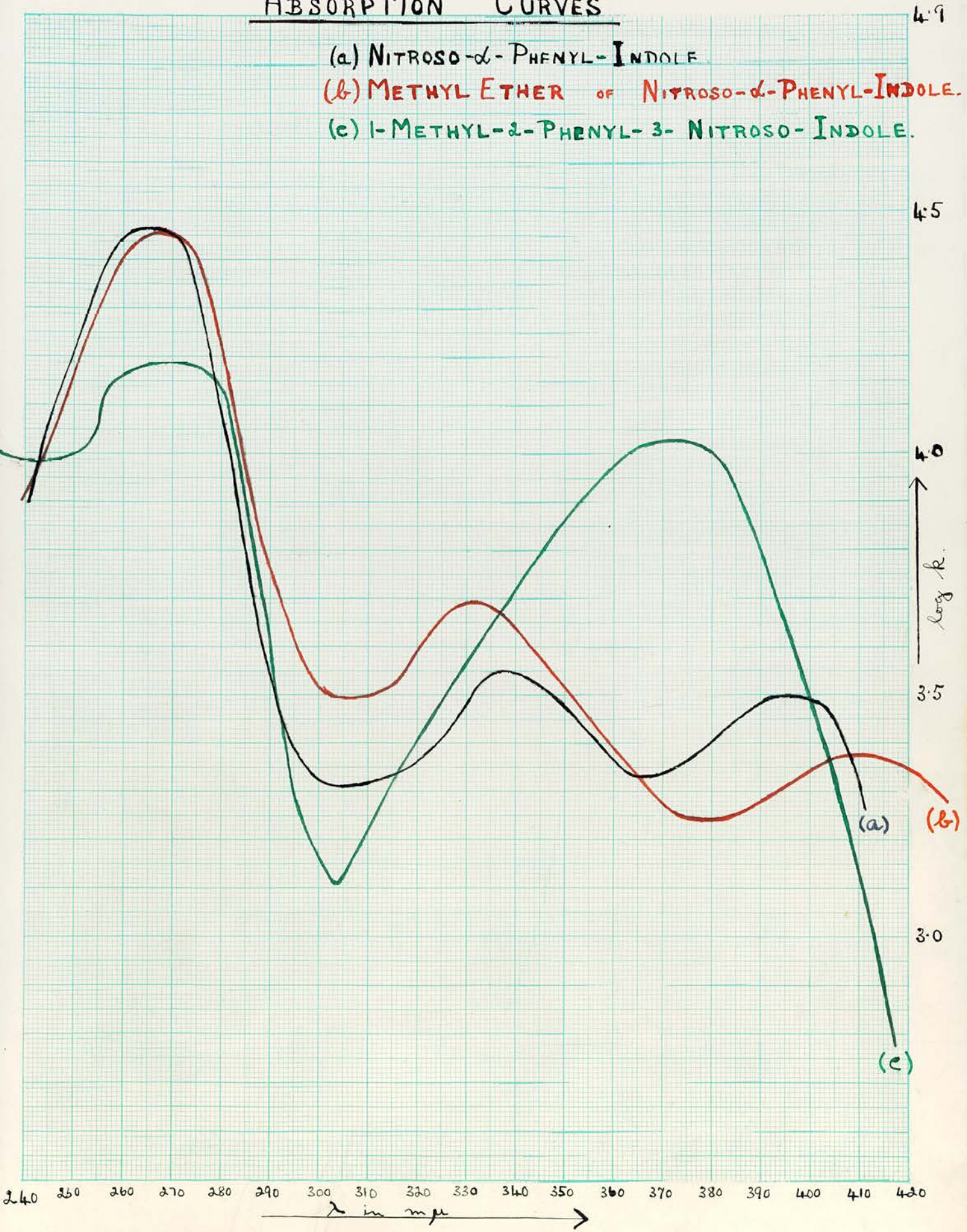
It is evident, therefore, that if "nitroso"-α-phenyl indole is a tautomeric mixture, which does not seem likely, the proportion of the true nitroso form must be very small. Actually, since there is no evidence whatever left in favour of the latter, it must be concluded that this substance (and therefore presumably the "nitroso-compounds" of all other 2-substituted -1:3-unsubstituted indoles) possesses the isonitroso structure only.

Absorption Curves

(a) Nitroso-α-Phenyl-Indole

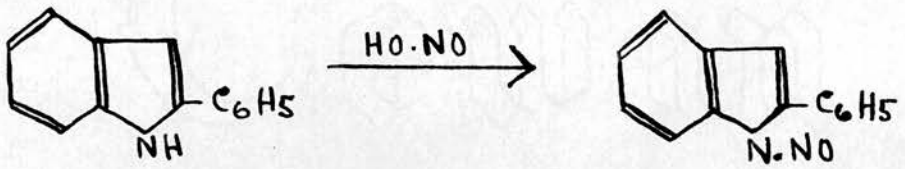
(b) Methyl Ether of Nitroso-α-Phenyl-Indole.

(c) 1-Methyl-2-Phenyl-3-Nitroso-Indole.



DISCUSSION.

The action of nitrous acid on indole and its derivatives represents a somewhat complex question which even yetcannot be considered completely solved. It might be expected that the indoles, being virtually secondary amines, would yield simple nitrosamines when treated with nitrous acid.
e.g.



This, however, only occurs where the 3-position is blocked by a substituent - otherwise the -NO group enters the indole nucleus in that position. The substances formed in the latter case, however, are isonitroso-compounds and not true nitroso-compounds, a subject which has just been discussed in detail. This type of compound can only result where the hydrogen atom of the imino-group remains unsubstituted, and if the latter is replaced by a methyl group a true 3-nitroso compound (green) is produced.

Three types of indole nitroso-compounds are therefore known, the N-nitrosamines, the 3-isonitroso compounds and the 3-nitroso compounds. All 3-substituted and 2:3- disubstituted indoles give the first type, the compounds being yellow solids of low melting-point, easily soluble in the common solvents and yielding the parent indoles on reduction. The 3-isonitroso compounds are given by 2- substituted indoles/

indoles and are remarkable for their high melting-points and insolubility, while, unlike the nitrosamines, they do not give the Liebermann reaction, and are reduced to amino-compounds instead of to the parent indoles.

The 3-nitroso-compounds appear to represent a previously unknown type. The only one prepared was remarkable for its brilliant emerald green colour, and failure to exhibit the characteristic reactions of nitrosobenzene. The reduction of the compound was not studied.

It is therefore evident that the type of "nitroso-compound" produced by the action of nitrous acid on any indole would appear to depend solely on which of the positions 1, 2, and 3 are already occupied by substituents. Despite the regularities traced above however, many inexplicable observations are recorded in the literature.

For example, N-methyl indole, which would be expected to yield a true nitroso compound (green) gives instead a substance strongly resembling the 3-isonitroso-compounds (Fischer and Hess, Ber., 1884, 17, 559). Further, the nitroso-compound of α-methyl indole does not appear to correspond to that of α-phenyl indole, since it changes in air, is soluble in alcohol, and gives a dark brown solution in glacial acetic acid (Spica and Angelico, Gazz., 1899, 29, 51).

Moreover, the structure of nitroso-indole itself is disputed. Zatti and Ferratini (Ber., 1890, 23, 2299) formulate the compound as a nitrosamine, claiming/

claiming that it gives the Liebermann reaction, yields indole on reduction, explodes feebly when heated on platinum foil and dissolves with decomposition in all solvents except acetone. Its high melting-point (171°-172° (d.)) they attribute to polymerisation, a statement which they substantiate by means of molecular weight determinations. This last point is contradicted, however, by Angeli and Marchetti (Atti R.A.L., 1907, 16, 381), whose experiments only gave the single formula, and who, having prepared the substance by the action of sodium ethoxide and amyl nitrite on indole, therefore formulate it as 3-iso nitroso-indole.

Finally, even 1:2:3- trisubstituted indoles react with nitrous acid, the latter probably adding on at the double bond in the 2:3- position (Fischer, Ann., 1886, 236, 116).

It is therefore evident that much work remains to be done in this field in order to correlate and explain the above conflicting observations, a subject which would have been taken up in this research had the exigencies of time permitted.

SUMMARY and CONCLUSION.

α-Phenyl indole and its Bz-methyl homologues have been prepared and examined, and four methods of synthesis studied and compared, namely those of Trennkler, Bischler, Fischer and Madelung. A new set of derivatives of the above five indoles has been obtained, and the identification of these substances placed on a more satisfactory footing. In this connection it is claimed that the previously utilised "nitroso-compounds" have now, for the first time, been isolated in a state of purity, thus enabling them to be employed for characterisation purposes. This result is due to a new purification process.

The oxidation of "nitroso"-α-phenyl-m-toluindole has been studied, with the object of orientating the methyl group, but this aim was in the end only achieved by an alternative synthesis of the parent indole. Arising from the attempts to prepare 2-phenyl-4-methyl indole from ortho-xylidine by Madelung's method, a detailed examination has been made of the literature methods of obtaining the latter substance from the "technical" product, and the definite conclusion has been reached that these methods are unsound, the fraction described as 3-amino-o-xylene being mainly 4-amino-m-xylene.

The mechanism of the Fischer synthesis has been discussed at some length, while experimental observations are advanced which are in strong opposition/

opposition to the theory of Reddelien. Unsuccessful attempts have also been made to test Robinson's theory, which, it is concluded, is the only one in satisfactory agreement with the available experimental evidence.

The structure of the "nitroso-compounds" has been investigated, and the views of Angeli fully substantiated, although it has now been shown (this thesis) that the evidence on which Angeli based his arguments is inadmissible. The formulation of "nitroso"-α-phenyl indole (and presumably, therefore, of the "nitroso-compounds" of all 2-phenyl-substituted -1:3-unsubstituted indoles) as an isonitroso-compound or oxime is now based (1) on the preparation of the substance by the action of hydroxylamine on the corresponding ketone (2-phenyl indolone), and (2) on the comparison of its absorption spectrum with those of its methyl ether and of the newly prepared 1-methyl-2-phenyl-3-nitroso indole.

The latter compound represents a previously unknown type of indole nitroso-compound, since it definitely possesses the C-NO structure and is green in colour. It does not, however, exhibit any of the typical reactions of nitrosobenzene.

In conclusion, the author desires to express his appreciation of the advice and guidance of Dr. Neil Campbell and Dr. H.G. Rule, whose friendly interest and enthusiasm could always be relied on.

INDEX to PREPARATIONS.

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